PATENT
Docket No. 219002028402

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Tami M. Procopio

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Sarvajit Chakravarty, *et al.*

Serial No.: Not yet assigned
Continuation of 09/383,825

Filing Date: Herewith

For: QUINAZOLINE DERIVATIVES AS MEDICAMENTS

Examiner: Not yet assigned,
Parent assigned to Hong Liu

Group Art Unit: Not yet assigned,
Parent in 1624

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to examination, please amend the specification as follows:

Enclosed is the following Exhibit A:

Exhibit A: Marked-up Version of Amendments to the Specification and Claims.

sd-53632

AMENDMENT

In the Specification:

On page 1 of the specification, under the title, please insert:

--This application is a continuation of U.S. Serial No. 09/383,825 filed 27 August 1999, which is a continuation-in-part of U.S. Serial No. 09/141,916 filed 28 August 1998. The contents of these applications are incorporated herein by reference.--

On page 10, replace the current second paragraph, at lines 5-21, with the following:

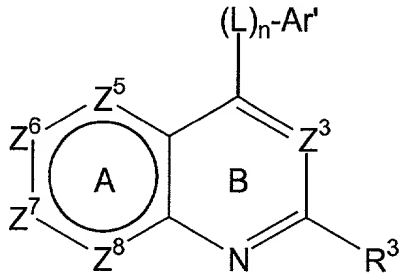
Each R^2 is also independently a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N. Preferably, R^2 is independently H, alkyl, alkenyl, alkynyl, acyl or hetero-forms thereof or is aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, NRSOR, $NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, NRSOR, $NRSO_2R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C). The aryl or aroyl groups on said substituents may be further substituted by, for example, alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C). More preferably the substituents on R^2 are selected from R^4, halo, OR^4, $NR^4{}_2$, SR^4, $-OOCR^4$, $-NR^4OCR^4$, $-COOR^4$, R^4CO, $-CONR^4{}_2$, $-SO_2NR^4{}_2$, CN, CF_3, and NO_2, wherein each R^4 is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R^4 or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

In the Claims:

Please amend the claims as follows:

Please replace the presently pending claims with the following claims:

1. (Amended) A method to inhibit p38α activity, which method comprises contacting said p38α with a compound of the formula:



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3 comprises a substituted or unsubstituted aromatic moiety, wherein said aromatic moiety is a monocyclic or fused bicyclic moiety containing 5-12 ring member atoms, optionally comprising one or more heteroatoms selected from O, S and N;

each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

each R^2 is either

(i) independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyl, wherein each of alkyl, alkenyl, alkynyl and acyl may optionally contain 1-2 O, S or N, aryl, and arylalkyl, each of said aryl and arylalkyl optionally containing 1 or more O, S or N and wherein in each of the foregoing other than H may be unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C), and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C), or

(ii) independently selected from the group consisting of halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, NRSOR, $NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, NRSOR, $NRSO_2R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C);

wherein L is a divalent moiety that provides a distance of 2-8Å between ring B and Ar';

n is 0 or 1; and

Ar' is a cyclic aliphatic, cyclic heteroaliphatic or a monocyclic or polycyclic aromatic moiety any of the foregoing optionally substituted with 1-3 substituents, wherein two of said substituents may form a 5-7 member cyclic optionally heterocyclic aliphatic ring and wherein Ar' and any said substituents thereon forming a cyclic aliphatic ring, may optionally contain one or more ring atoms selected from O, S and N.

Please cancel claims 2-7.

8. (Amended) The method of claim 1 wherein any substituents on the aromatic or heteroaromatic moiety of R^3 are independently selected from the group consisting of halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C) and alkyl (1-6C).

9. The method of claim 1 wherein said substituents on substituted Ar' are independently selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C),

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C).

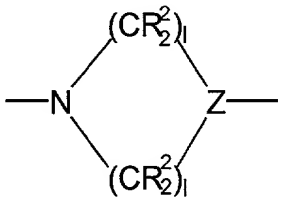
10. (Amended) The method of claim 9 wherein Ar' is phenyl, 2-, 3-, or 4-pyridyl, 2- or 4-pyrimidyl, indolyl, isoquinolyl, quinolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzofuranyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, or imidazolyl, all of which may optionally be substituted.

Please cancel claims 11 and 12.

13. (Amended) The method of claim 1 wherein said optional substituents on R^2 are independently selected from the group consisting of R^4, halo, OR^4, NR^4_2, SR^4, $-OOCR^4$, $-NROCR^4$, $-COOR^4$, R^4CO, $-CONR^4_2$, $-SO_2NR^4_2$, CN, CF_3, and NO_2, wherein each R^4 is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R^4 or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

Please cancel claim 14.

15. (Amended) The method of claim 1 wherein L is $S(CR^2_2)_m$, $-NR^1SO_2(CR^2_2)_l$, $SO_2(CR^2_2)_m$, $SO_2NR^1(CR^2_2)_l$, $NR^1(CR^2_2)_m$, $NR^1CO(CR^2_2)_l$, $O(CR^2_2)_m$, or $OCO(CR^2_2)_l$, or



wherein Z is N or CH and wherein m is 0-4 and l is 0-3;

R^1 is H, alkyl or arylalkyl where the aryl moiety may be substituted by 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C);

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$,

-NRCOOR, -NRSOR, -$NRSO_2R$, -$OCONR_2$, RCO, -COOR, -SO_3R, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C); and

R^2 is as defined in claim 1.

16. (Amended) The method of claim 1 wherein the compound of formula (1) is selected from group consisting of

(a) the compounds listed in Table 2 below, wherein Z^5-Z^8 are CH; Z^3 is N; R^1 in compound No. 11 is 2-propyl; R^1 in compound No. 12 is 4-methoxyphenyl, and R^1 in compound No. 41 is 4-methoxybenzyl; and wherein L, Ar' and R^3 are as shown in Table 2:

Table 2

Compound No.	L	Ar'	R^3
1	NH	4-pyridyl	2-chlorophenyl
2	NH	4-pyridyl	2,6-dichlorophenyl
3	NH	4-pyridyl	2-methylphenyl
4	NH	4-pyridyl	2-bromophenyl
5	NH	4-pyridyl	2-fluorophenyl
6	NH	4-pyridyl	2,6-difluorophenyl
7	NH	4-pyridyl	phenyl
8	NH	4-pyridyl	4-fluorophenyl
9	NH	4-pyridyl	4-methoxyphenyl
10	NH	4-pyridyl	3-fluorophenyl
11	NR^1	4-pyridyl	phenyl
12	NR^1	4-pyridyl	phenyl
13	$NHCH_2$	4-pyridyl	phenyl
14	$NHCH_2$	4-pyridyl	4-chlorophenyl
15	NH	3-pyridyl	phenyl
16	$NHCH_2$	2-pyridyl	phenyl
17	$NHCH_2$	3-pyridyl	phenyl
18	$NHCH_2$	2-pyridyl	phenyl
19	$NHCH_2CH_2$	2-pyridyl	phenyl
20	NH	6-pyrimidinyl	phenyl
21	NH	2-pyrimidinyl	phenyl
22	NH	Phenyl	phenyl
23	$NHCH_2$	Phenyl	3-chlorophenyl
24	NH	3-hydroxyphenyl	phenyl
25	NH	2-hydroxyphenyl	phenyl

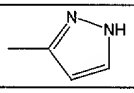
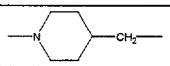
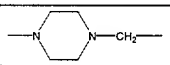
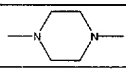
Table 2			
Compound No.	**L**	**Ar'**	**R^3**
26	NH	4-hydroxyphenyl	phenyl
27	NH	4-indolyl	phenyl
28	NH	5-indolyl	phenyl
29	NH	4-methoxyphenyl	phenyl
30	NH	3-methoxyphenyl	phenyl
31	NH	2-methoxyphenyl	phenyl
32	NH	4-(2-hydroxyethyl)phenyl	phenyl
33	NH	3-cyanophenyl	phenyl
34	$NHCH_2$	2,5-difluorophenyl	phenyl
35	NH	4-(2-butyl)phenyl	phenyl
36	$NHCH_2$	4-dimethylaminophenyl	phenyl
38	NH	2-pyridyl	phenyl
39	$NHCH_2$	3-pyridyl	phenyl
40	NH	4-pyrimidyl	phenyl
41	NR^1	4-pyridyl	phenyl
42	NH	p-aminomethylphenyl	phenyl
43	$NHCH_2$	4-aminophenyl	phenyl
44	NH	4-pyridyl	3-chlorophenyl
45	NH	Phenyl	4-pyridyl
46	NH		phenyl
48	NH	2-benzylamino-3-pyridyl	phenyl
49	NH	2-benzylamino-4-pyridyl	phenyl
50	NH	3-benzyloxyphenyl	phenyl
51	NH	4-pyridyl	3-aminophenyl
52	NH	4-pyridyl	4-pyridyl
53	NH	4-pyridyl	2-naphthyl
54		4-pyridyl	phenyl
55		Phenyl	phenyl
56		2-pyridyl	phenyl
61	NH	4-pyridyl	2-trifluoromethyl phenyl
62	NH	4-aminophenyl	phenyl
64	NH	3-methoxyphenyl	2-fluorophenyl
65	NH	4-methoxyphenyl	2-fluorophenyl

Table 2			
Compound No.	**L**	**Ar'**	**R^3**
66	NH	4-pyrimidinyl	2-fluorophenyl
67	NH	3-amino-4-pyridyl	phenyl
68	NH	4-pyridyl	2-benzylaminophenyl
69	NH	2-benzylaminophenyl	phenyl
70	NH	2-benzylaminophenyl	4-cyanophenyl
71	NH	3'-cyano-2-benzylaminophenyl	phenyl

(b) the compounds listed in Table 3, below, wherein L is NH; Z^3 is N; Z^6 and Z^7 are CH and Z^5, Z^8, Ar' and R^3 are as shown in Table 3:

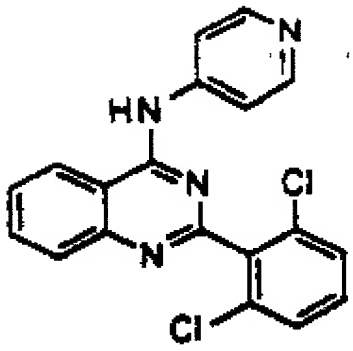
Table 3				
Compound No.	**Z^5**	**Z^8**	**Ar'**	**R^3**
72	CH	N	4-pyridyl	2-fluorophenyl
73	CH	N	4-pyridyl	2-chlorophenyl
74	CH	N	4-pyridyl	phenyl
75	N	N	4-pyridyl	phenyl
76	N	CH	4-pyridyl	phenyl

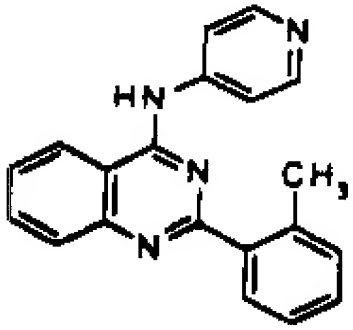
and

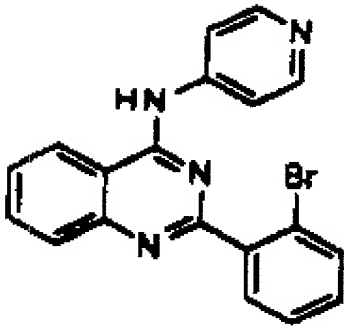
(c) the quinazoline derivatives listed in Table 4 below, wherein L is NH; Ar' is 4-pyridyl; Z^3, Z^5, and Z^8 are N; Z^6 or Z^7 are CR^2 as shown and each is otherwise N and wherein R^3 and R^2 are as shown in Table 4:

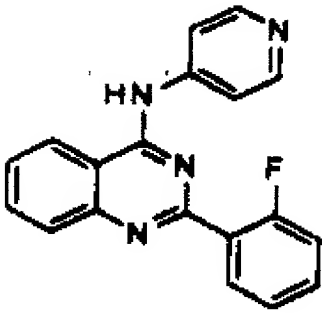
Table 4		
Compound No.	**R^3**	**R^2**
77	2-chlorophenyl	6,7-dimethoxy
78	2-fluorophenyl	6-nitro
79	2-fluorophenyl	6-amino
80	2-fluorophenyl	7-amino
81	2-fluorophenyl	6-(3-methoxybenzylamino)
82	2-fluorophenyl	6-(4-methoxybenzylamino)
83	2-fluorophenyl	6-(2-isobutylamino)
84	2-fluorophenyl	6-(4-methylmercaptobenzylamino)
85	2-fluorophenyl	6-(4-methoxybenzoyl amino)
86	4-fluorophenyl	7-amino
87	4-fluorophenyl	7-(3-methoxybenzylamino)

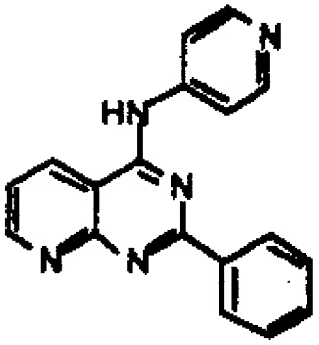
17. (Amended) The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of the following compounds:

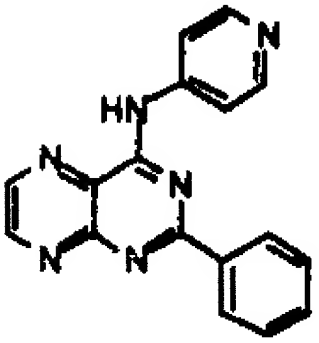


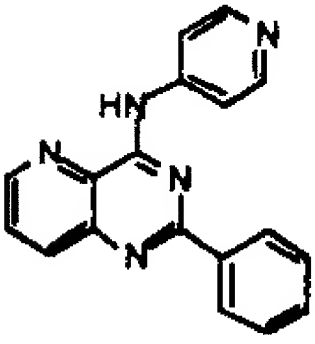


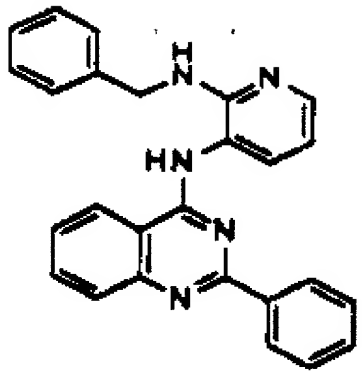


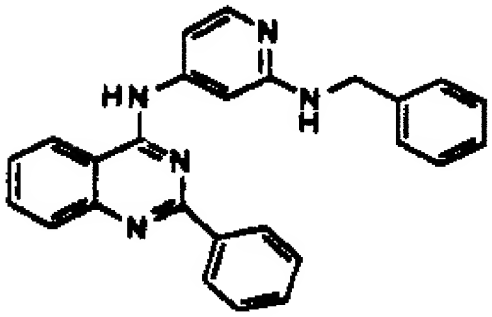


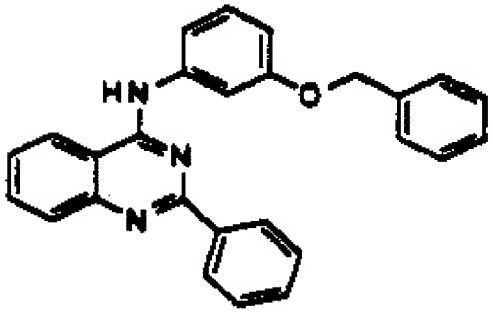


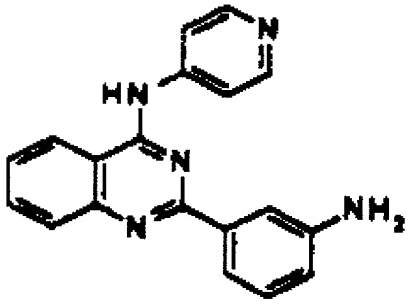


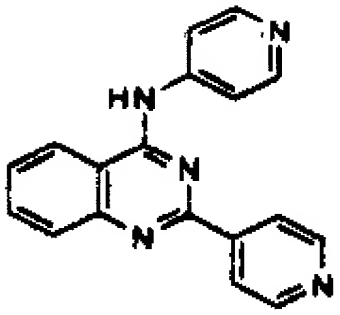


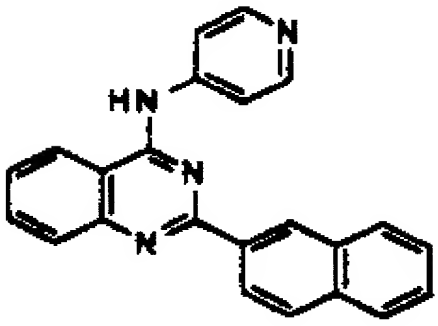


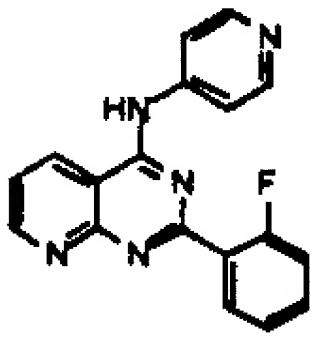


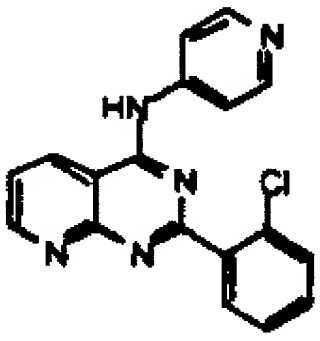












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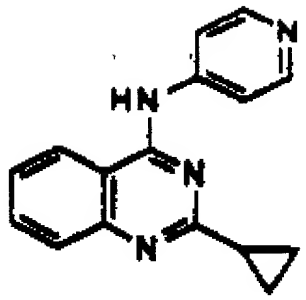

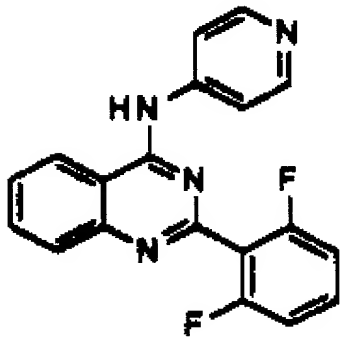

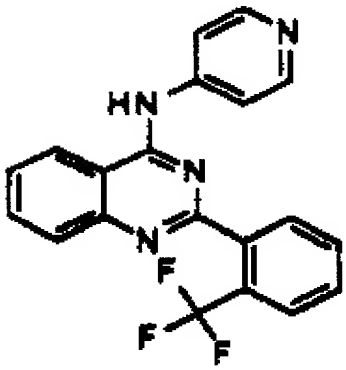

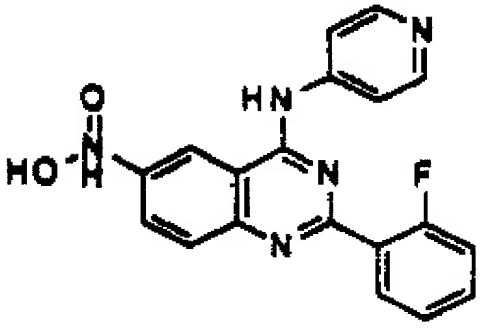

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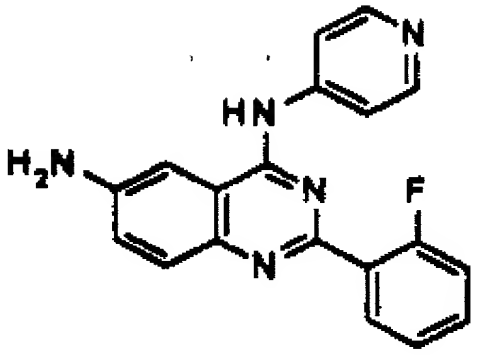

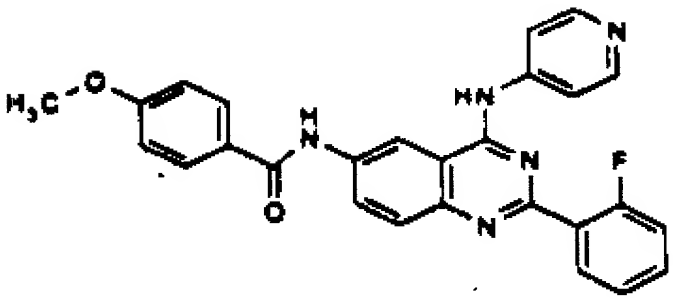

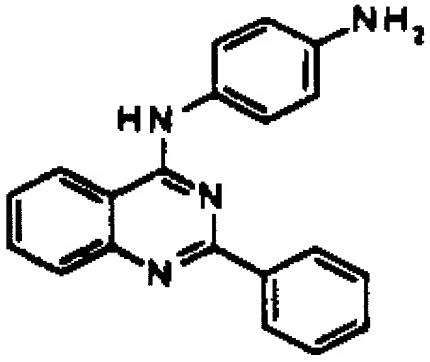

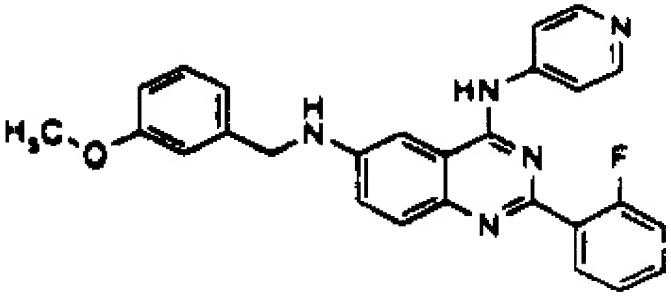

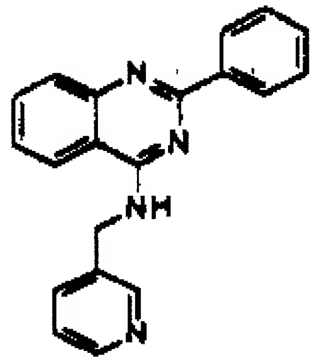

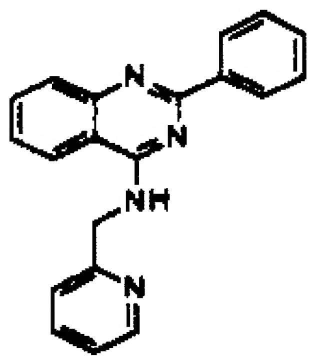

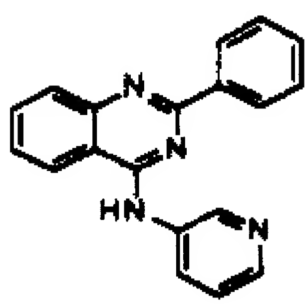

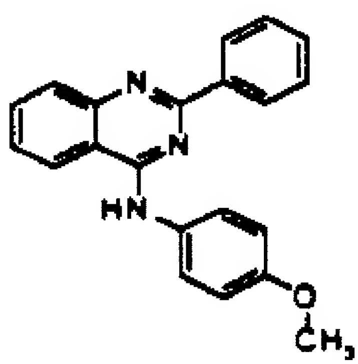

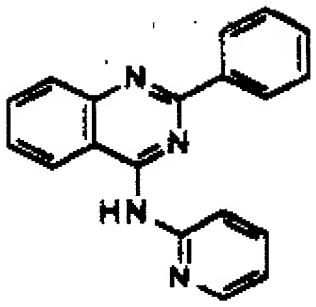

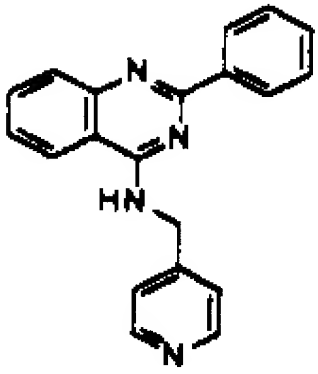

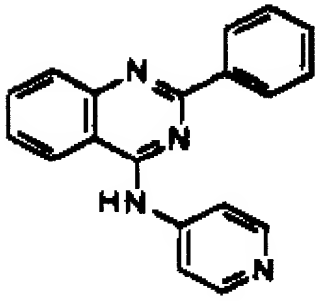

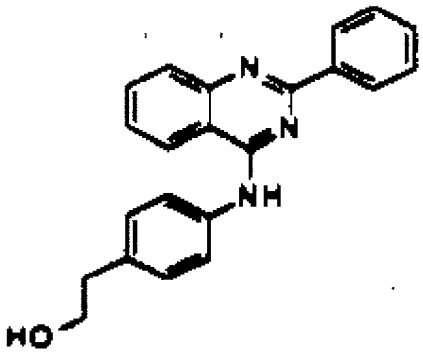

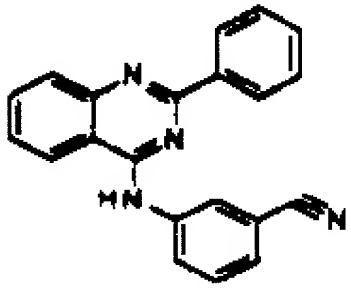

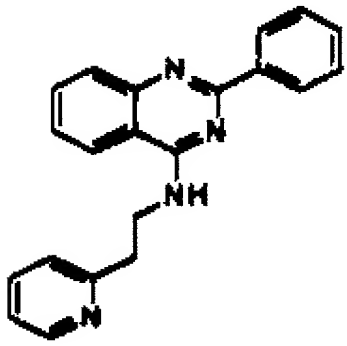

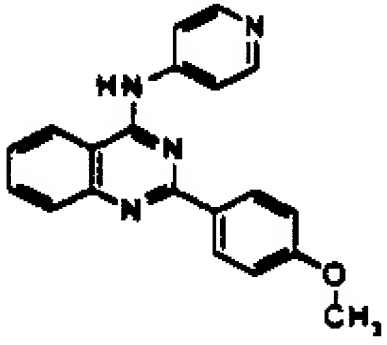

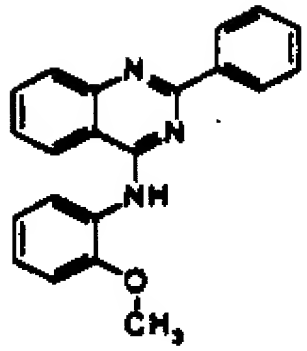

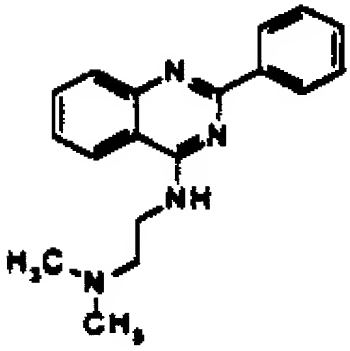

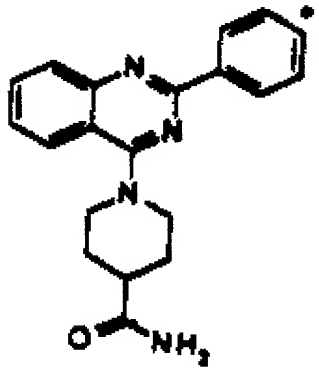

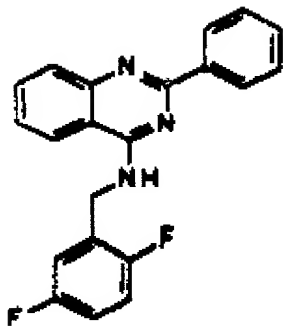

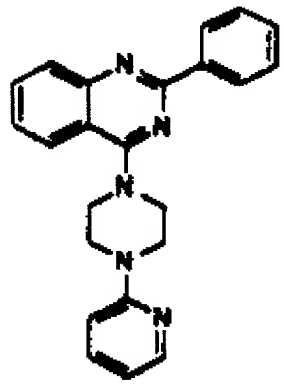

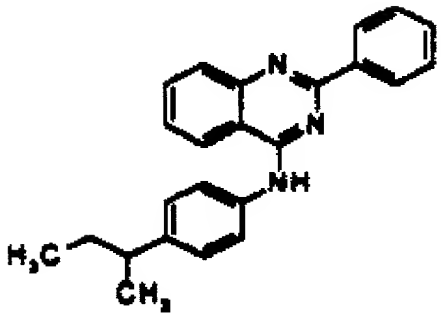

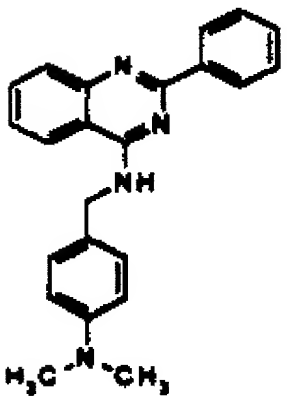

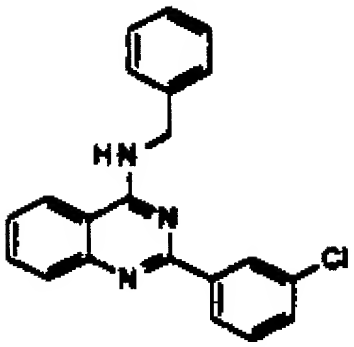

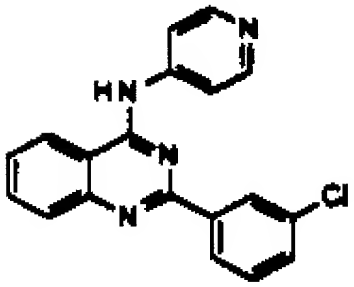

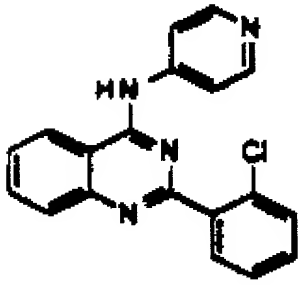

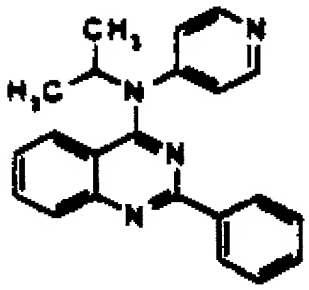

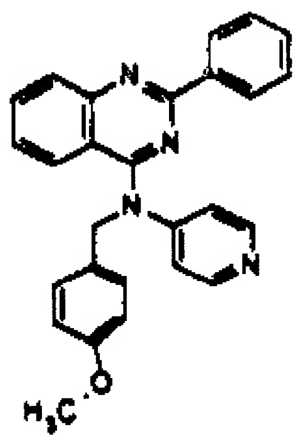
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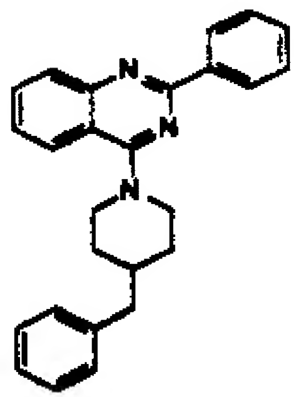
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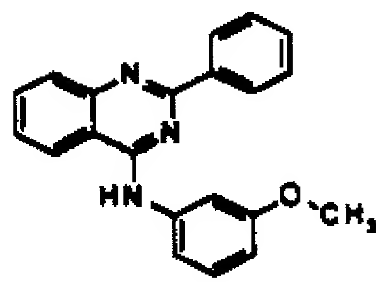
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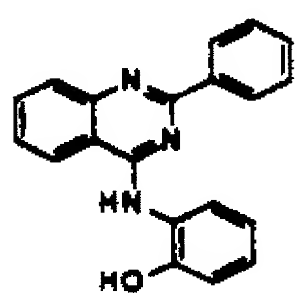
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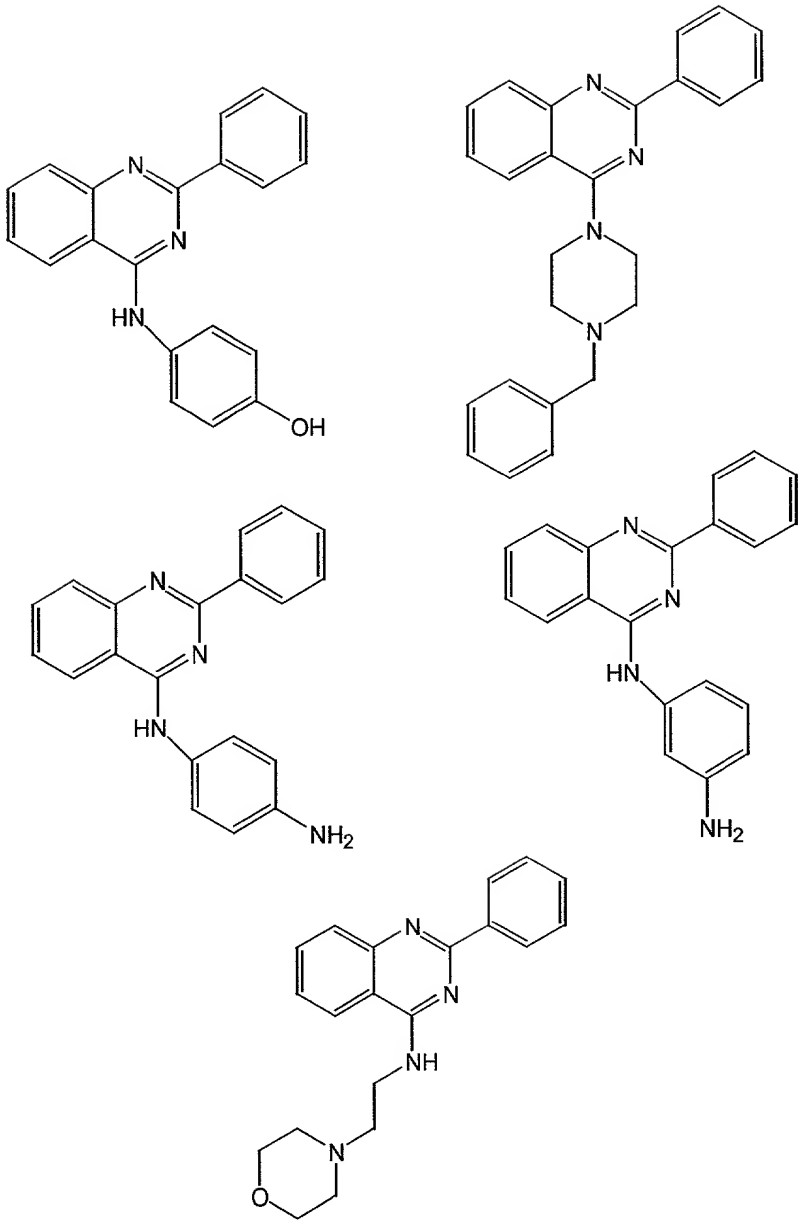
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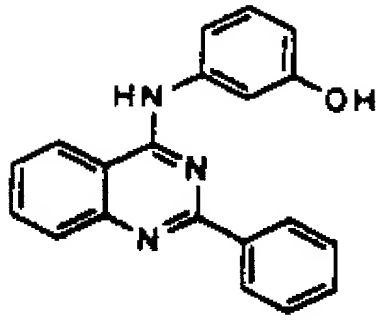
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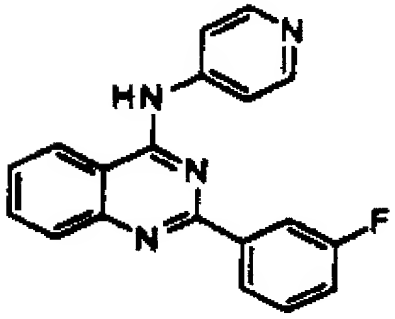
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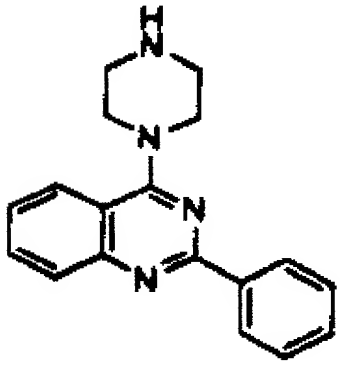
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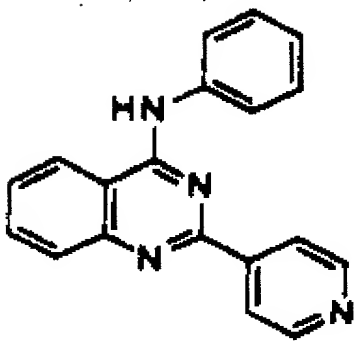
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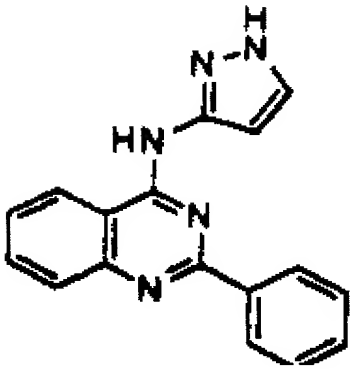
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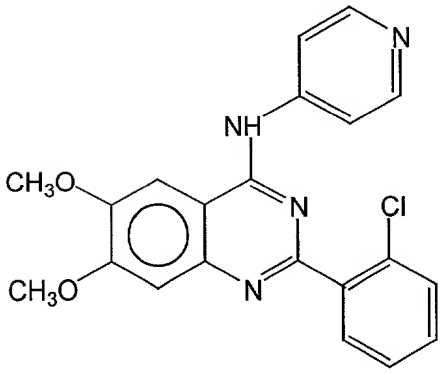
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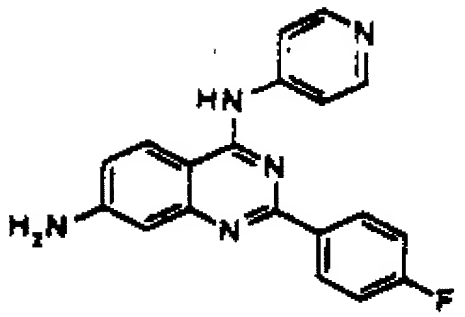

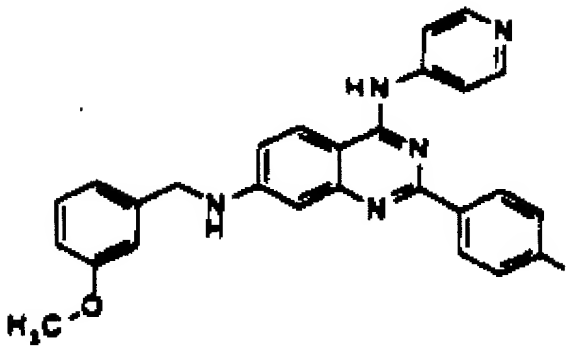

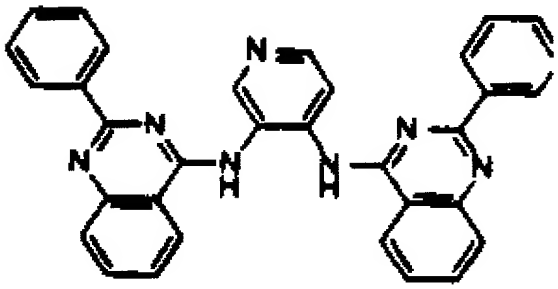

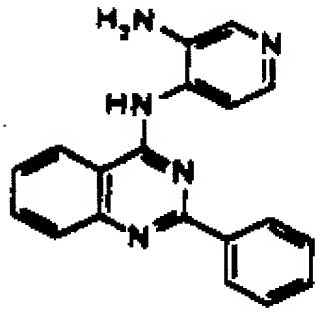

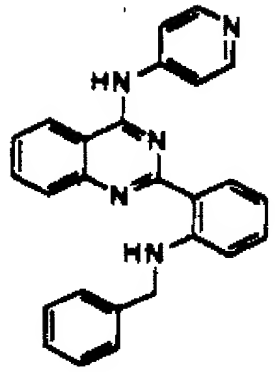

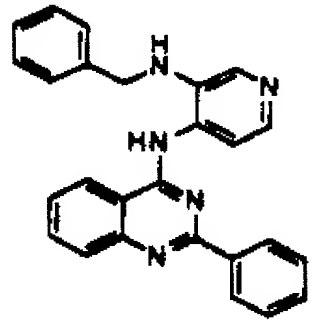

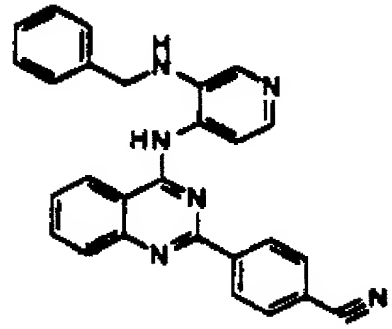

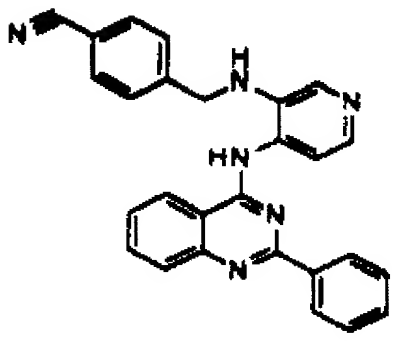

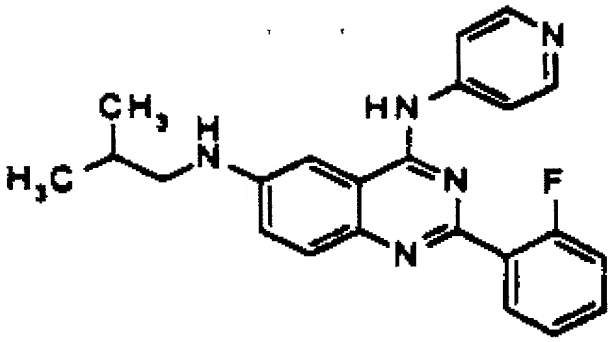

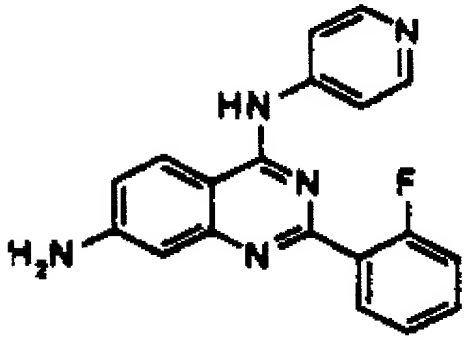

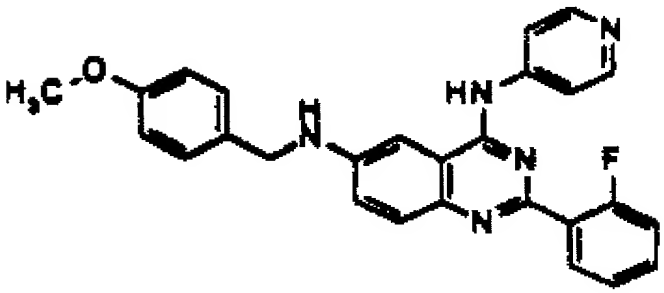

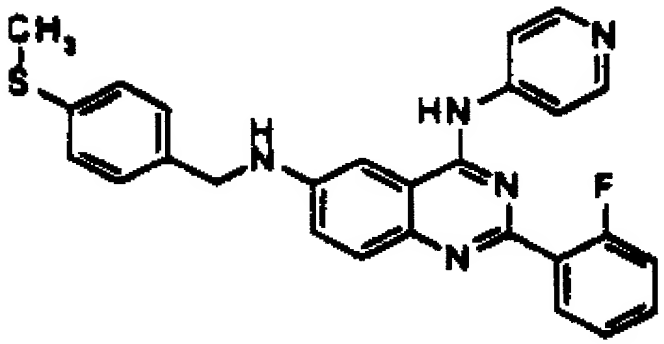

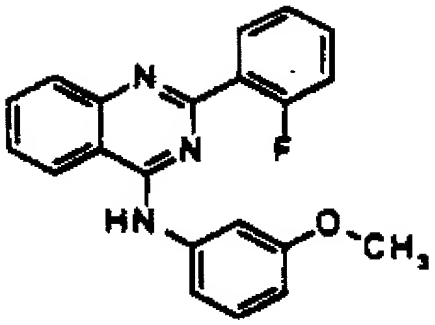

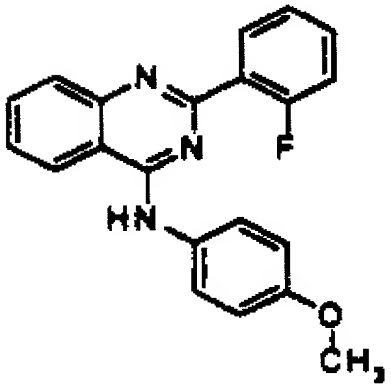

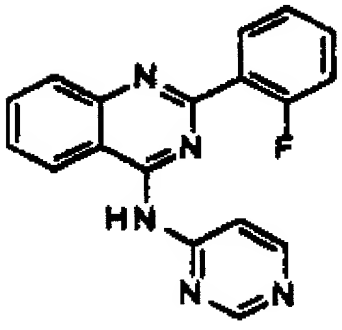

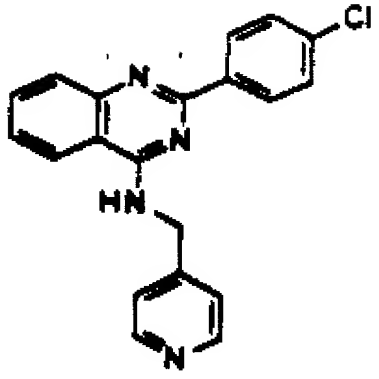
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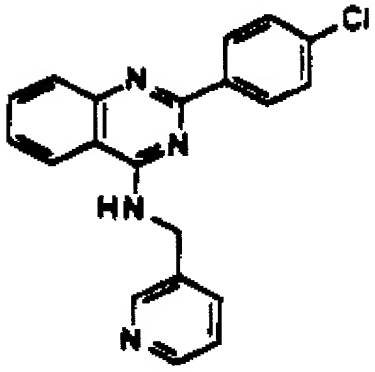
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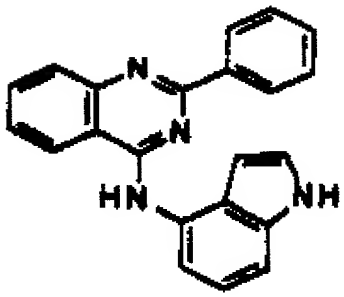
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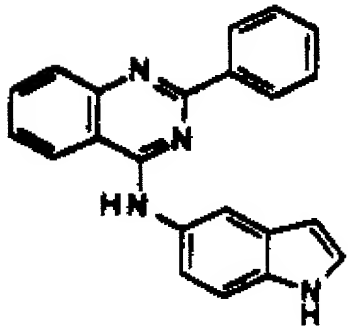
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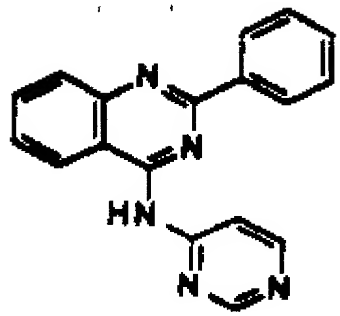
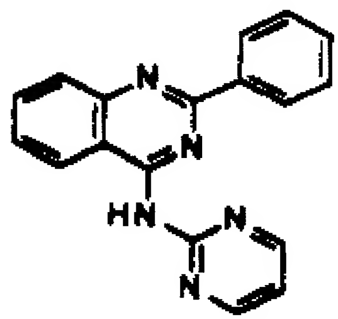
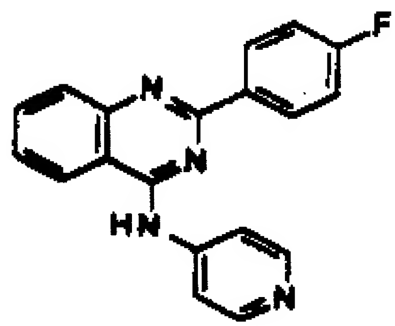
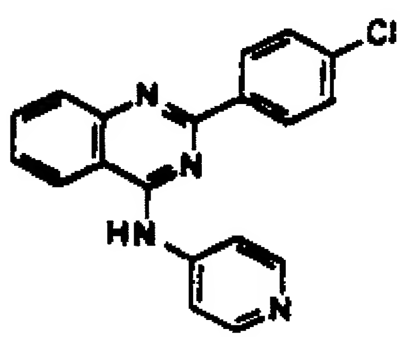






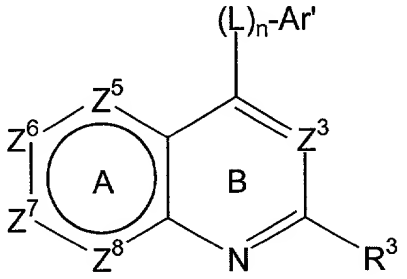


Serial No. Not yet assigned
Docket No. 219002028402

sd-53632

18. (Amended) A pharmaceutical composition for treating conditions characterized by enhanced p38α kinase activity which composition comprises

an amount of a compound of the formula



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3;

each Z;

each R^2;

L;

n; and

Ar' are as defined in claim 1 which is effective to inhibit p38α kinase activity in admixture with at least one pharmaceutically acceptable excipient appropriate for administering to a subject exhibiting enhanced p38α kinase activity.

19. The composition of claim 18 which further contains an additional therapeutic agent.

20. The composition of claim 19 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

Please cancel claims 21-22.

Please add the following claims:

23. (New) The method of claim 1 wherein

L is $-R^1N(CH_2)_n-$ wherein R^1 is H or is alkyl (1-6C) or arylalkyl optionally substituted on the aryl group with 1-3 substituents independently selected from alkyl (1-6C), halo, OR, NR_2,

SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, -SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C) and n is 0, 1 or 2; and

(a) Ar′ is phenyl, substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C), or pyridyl, indolyl, or pyrimidyl, each optionally substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is phenyl optionally substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, -SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or

(b) Ar′ is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is phenyl substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, -SO_2NR_2, CN, and CF_3, wherein each R is independently H or lower alkyl (1-4C); or

(c) Ar′ is phenyl substituted with a group selected from the group consisting of optionally substituted NR_2, SR, -NROCR, RCO, -$CONR_2$, SO_2NR_2, CN, and CF_3, wherein each R is independently H or lower alkyl (1-4C); or pyridyl substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or indolyl or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is phenyl optionally substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR,

-$CONR_2$, -SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or

(d) Ar′ is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is phenyl substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, -SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C).

24. (New) The method of claim 1 wherein the compound of formula 1 is selected from the group consisting of

2-phenyl-4-(4-pyridylamino)-quinazoline;

2-(2-bromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-chlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-methylphenyl)-4-(4-pyridylamino)-quinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(3-methoxyanilyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-dichlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-dibromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-difluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-nitroquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino -6-aminoquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-7-aminoquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(3-methoxybenzylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methoxybenzylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(2-isobutylamino)-quinazoline; and

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methylmercaptobenzylamino)-quinazoline.

25. (New) The composition of claim 18 wherein any substituents on the aromatic or heteroaromatic moiety of R^3 are independently selected from the group consisting of alkyl (1-6C), halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C).

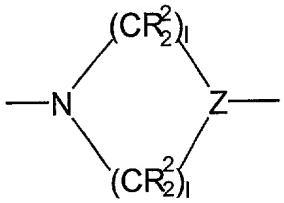
26. (New) The composition of claim 18 wherein said substituents on substituted Ar' are independently selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C),

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C).

27. (New) The composition of claim 26 wherein Ar' is phenyl, 2-, 3-, or 4-pyridyl, 2- or 4-pyrimidyl, indolyl, isoquinolyl, quinolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzofuranyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, or imidazolyl, all of which may optionally be substituted.

28. (New) The composition of claim 18 wherein said optional substituents on R^2 are independently selected from the group consisting of R^4, halo, OR^4, NR^4_2, SR^4, $-OOCR^4$, $-NROCR^4$, $-COOR^4$, R^4CO, $-CONR^4_2$, $-SO_2NR^4_2$, CN, CF_3, and NO_2, wherein each R^4 is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R^4 or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

29. (New) The composition of claim 18 wherein L is $S(CR^2_2)_m$, $-NR^1SO_2(CR^2_2)_l$, $SO_2(CR^2_2)_m$, $SO_2NR^1(CR^2_2)_l$, $NR^1(CR^2_2)_m$, $NR^1CO(CR^2_2)_l$, $O(CR^2_2)_m$, or $OCO(CR^2_2)_l$, or



wherein Z is N or CH and wherein m is 0-4 and l is 0-3;

R^1 is H, alkyl or arylalkyl where the aryl moiety may be substituted by 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C);

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C); and

R^2 is as defined in claim 18.

30. (New) The composition of claim 18 wherein the compound of formula (1) is selected from the group consisting of

(a) the compounds listed in Table 2 below, wherein Z^5-Z^8 are CH; Z^3 is N; R^1 in compound No. 11 is 2-propyl; R^1 in compound No. 12 is 4-methoxyphenyl, and R^1 in compound No. 41 is 4-methoxybenzyl; and wherein L, Ar' and R^3 are as shown in Table 2:

Table 2

Compound No.	L	Ar'	R^3
1	NH	4-pyridyl	2-chlorophenyl
2	NH	4-pyridyl	2,6-dichlorophenyl
3	NH	4-pyridyl	2-methylphenyl
4	NH	4-pyridyl	2-bromophenyl
5	NH	4-pyridyl	2-fluorophenyl
6	NH	4-pyridyl	2,6-difluorophenyl

Table 2			
Compound No.	**L**	**Ar'**	**R^3**
7	NH	4-pyridyl	phenyl
8	NH	4-pyridyl	4-fluorophenyl
9	NH	4-pyridyl	4-methoxyphenyl
10	NH	4-pyridyl	3-fluorophenyl
11	NR^1	4-pyridyl	phenyl
12	NR^1	4-pyridyl	phenyl
13	$NHCH_2$	4-pyridyl	phenyl
14	$NHCH_2$	4-pyridyl	4-chlorophenyl
15	NH	3-pyridyl	phenyl
16	$NHCH_2$	2-pyridyl	phenyl
17	$NHCH_2$	3-pyridyl	phenyl
18	$NHCH_2$	2-pyridyl	phenyl
19	$NHCH_2CH_2$	2-pyridyl	phenyl
20	NH	6-pyrimidinyl	phenyl
21	NH	2-pyrimidinyl	phenyl
22	NH	Phenyl	phenyl
23	$NHCH_2$	Phenyl	3-chlorophenyl
24	NH	3-hydroxyphenyl	phenyl
25	NH	2-hydroxyphenyl	phenyl
26	NH	4-hydroxyphenyl	phenyl
27	NH	4-indolyl	phenyl
28	NH	5-indolyl	phenyl
29	NH	4-methoxyphenyl	phenyl
30	NH	3-methoxyphenyl	phenyl
31	NH	2-methoxyphenyl	phenyl
32	NH	4-(2-hydroxyethyl)phenyl	phenyl
33	NH	3-cyanophenyl	phenyl
34	$NHCH_2$	2,5-difluorophenyl	phenyl
35	NH	4-(2-butyl)phenyl	phenyl
36	$NHCH_2$	4-dimethylaminophenyl	phenyl
38	NH	2-pyridyl	phenyl
39	$NHCH_2$	3-pyridyl	phenyl
40	NH	4-pyrimidyl	phenyl
41	NR^1	4-pyridyl	phenyl
42	NH	p-aminomethylphenyl	phenyl
43	$NHCH_2$	4-aminophenyl	phenyl

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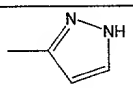
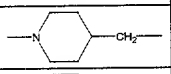
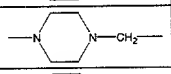
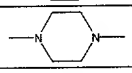
Table 2			
Compound No.	**L**	**Ar'**	**R^3**
44	NH	4-pyridyl	3-chlorophenyl
45	NH	Phenyl	4-pyridyl
46	NH		phenyl
48	NH	2-benzylamino-3-pyridyl	phenyl
49	NH	2-benzylamino-4-pyridyl	phenyl
50	NH	3-benzyloxyphenyl	phenyl
51	NH	4-pyridyl	3-aminophenyl
52	NH	4-pyridyl	4-pyridyl
53	NH	4-pyridyl	2-naphthyl
54		4-pyridyl	phenyl
55		Phenyl	phenyl
56		2-pyridyl	phenyl
61	NH	4-pyridyl	2-trifluoromethyl phenyl
62	NH	4-aminophenyl	phenyl
64	NH	3-methoxyphenyl	2-fluorophenyl
65	NH	4-methoxyphenyl	2-fluorophenyl
66	NH	4-pyrimidinyl	2-fluorophenyl
67	NH	3-amino-4-pyridyl	phenyl
68	NH	4-pyridyl	2-benzylaminophenyl
69	NH	2-benzylaminophenyl	phenyl
70	NH	2-benzylaminophenyl	4-cyanophenyl
71	NH	3'-cyano-2-benzylaminophenyl	phenyl

(b) the compounds listed in Table 3, below, wherein L is NH; Z^3 is N; Z^6 and Z^7 are CH and Z^5, Z^8, Ar' and R^3 are as shown in Table 3:

Table 3

Compound No.	Z^5	Z^8	Ar'	R^3
72	CH	N	4-pyridyl	2-fluorophenyl
73	CH	N	4-pyridyl	2-chlorophenyl
74	CH	N	4-pyridyl	phenyl
75	N	N	4-pyridyl	phenyl
76	N	CH	4-pyridyl	phenyl

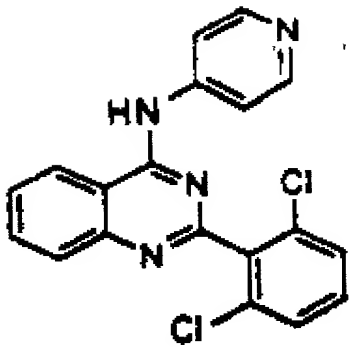
and

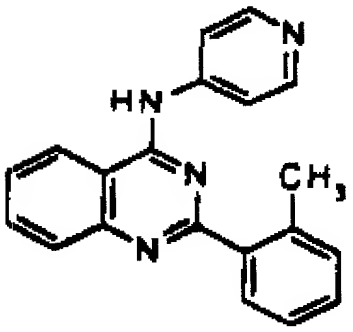
(c) the quinazoline derivatives listed in Table 4 below, wherein L is NH; Ar' is 4-pyridyl; Z^3, Z^5, and Z^8 are N; Z^6 or Z^7 are CR^2 as shown and each is otherwise N and wherein R^3 and R^2 are as shown in Table 4:

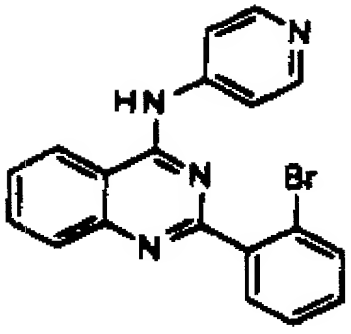
Table 4

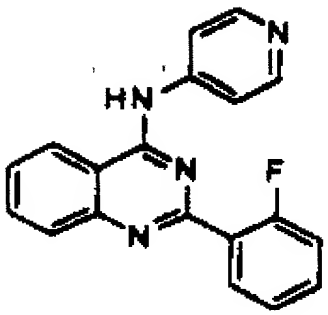
Compound No.	R^3	R^2
77	2-chlorophenyl	6,7-dimethoxy
78	2-fluorophenyl	6-nitro
79	2-fluorophenyl	6-amino
80	2-fluorophenyl	7-amino
81	2-fluorophenyl	6-(3-methoxybenzylamino)
82	2-fluorophenyl	6-(4-methoxybenzylamino)
83	2-fluorophenyl	6-(2-isobutylamino)
84	2-fluorophenyl	6-(4-methylmercaptobenzylamino)
85	2-fluorophenyl	6-(4-methoxybenzoyl amino)
86	4-fluorophenyl	7-amino
87	4-fluorophenyl	7-(3-methoxybenzylamino)

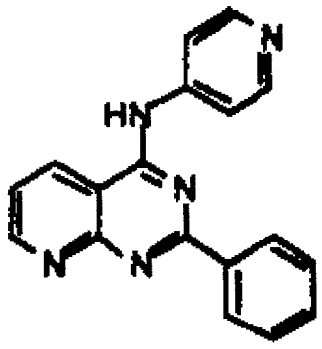
31. (New) The composition of claim 18 wherein the compound of formula (1) is selected from the group consisting of the following compounds:

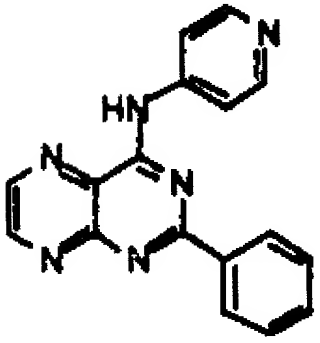

HN
N
N
N
Cl
Cl

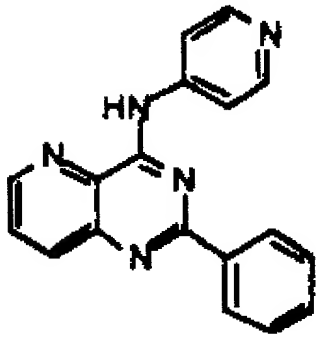

HN
N
N
N
CH3

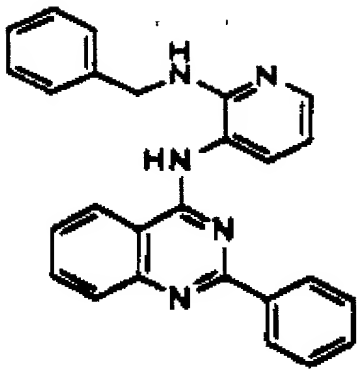

HN
N
N
N
Br

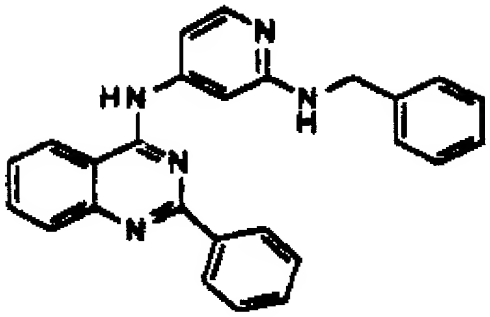


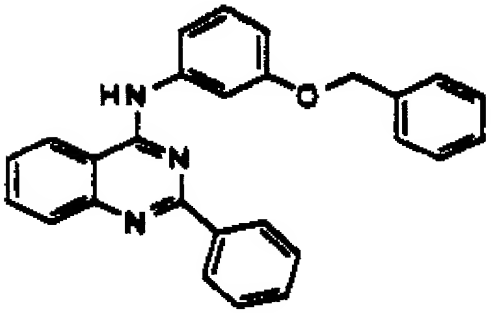


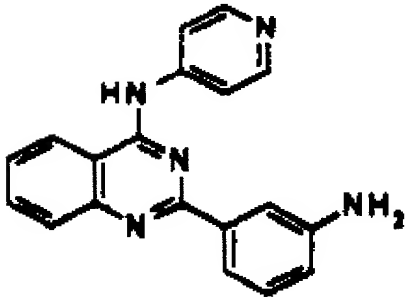


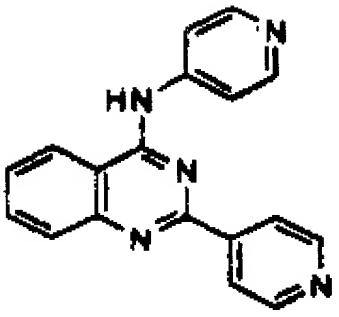


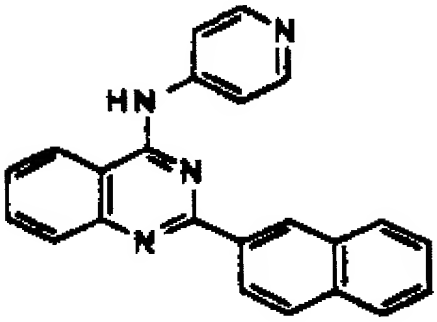


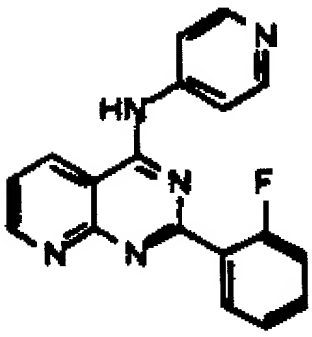


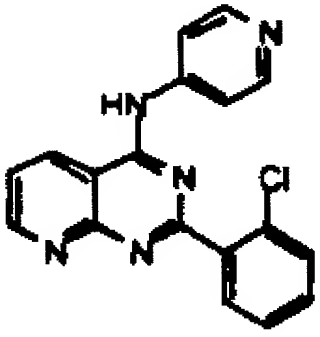


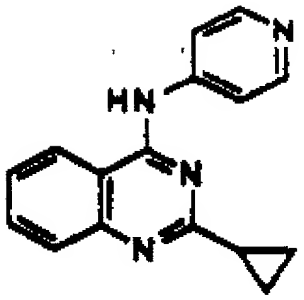


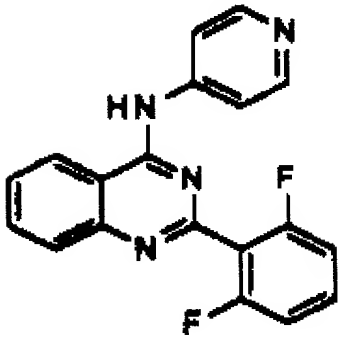


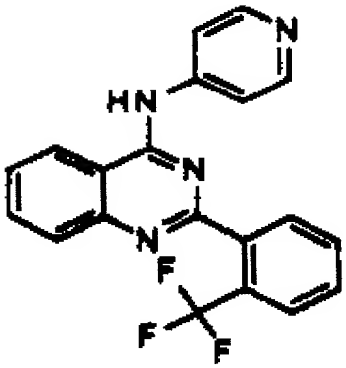


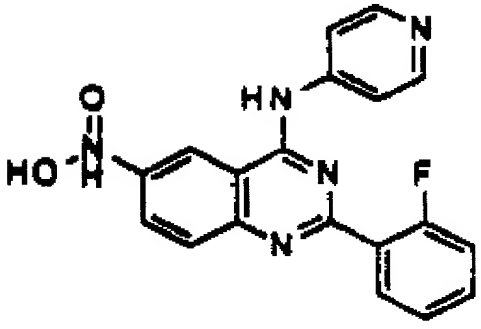


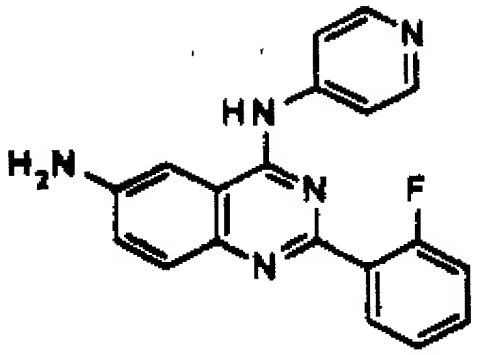


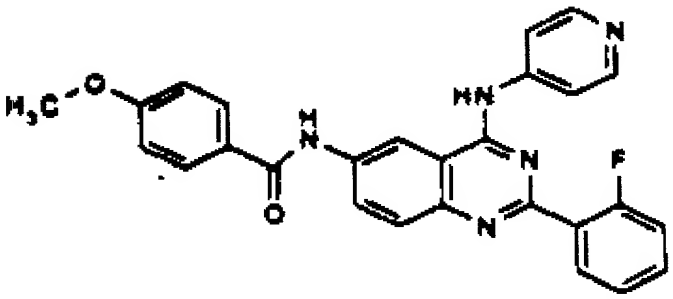


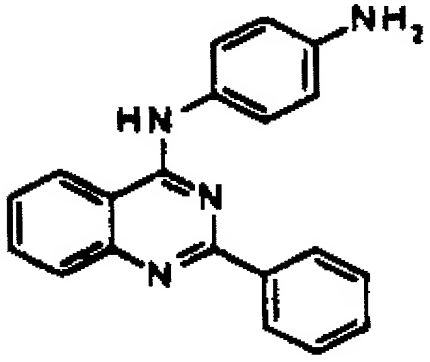


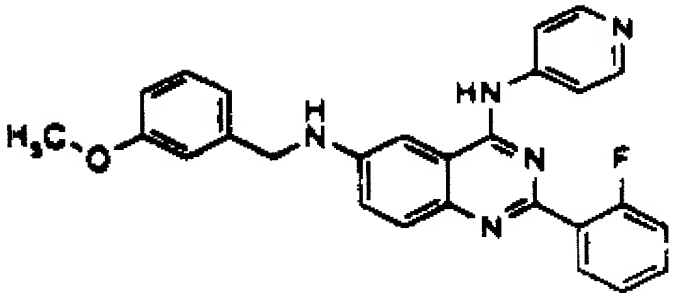


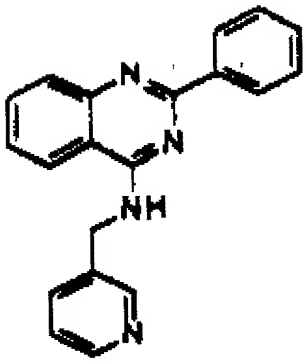


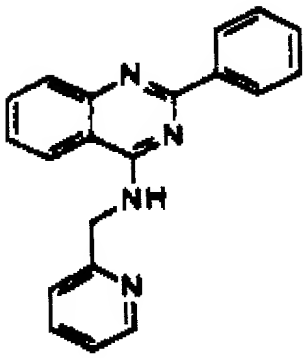


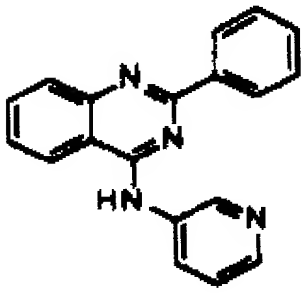


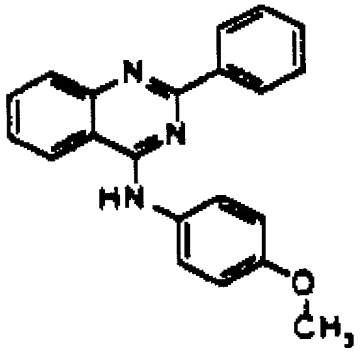


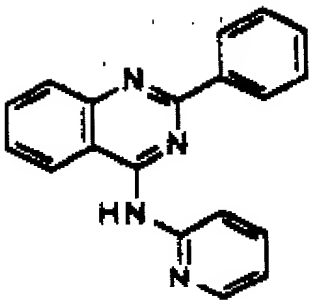


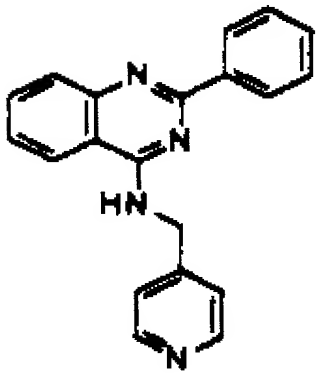


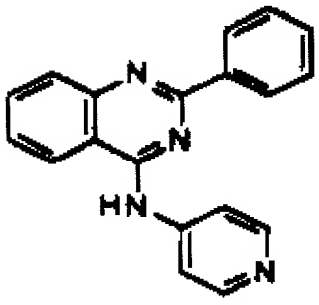


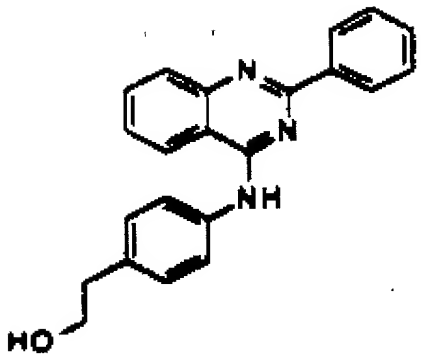


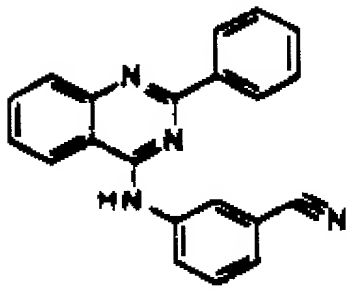


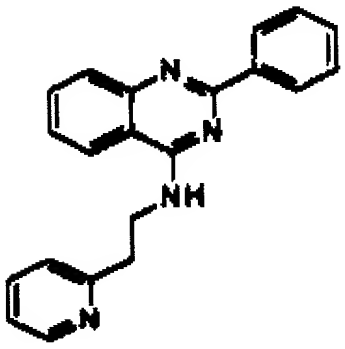


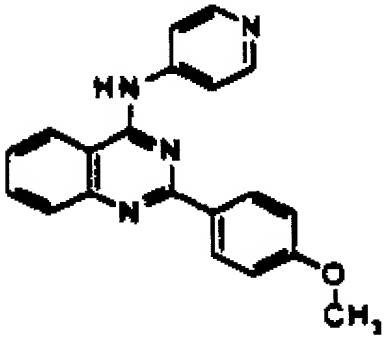


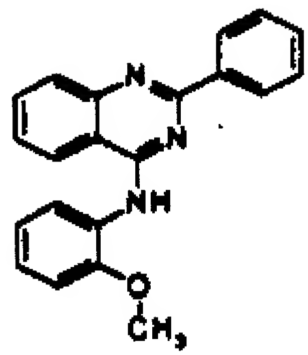








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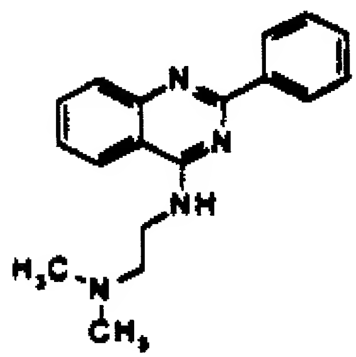
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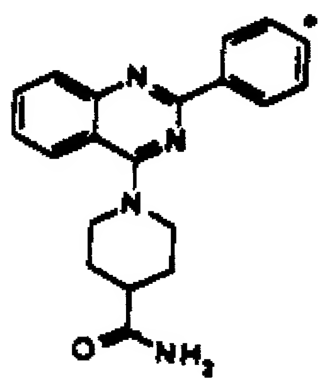
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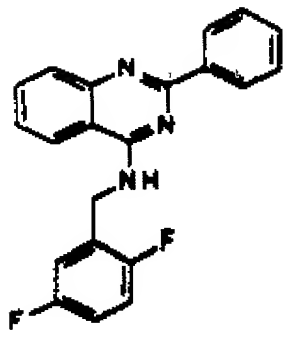

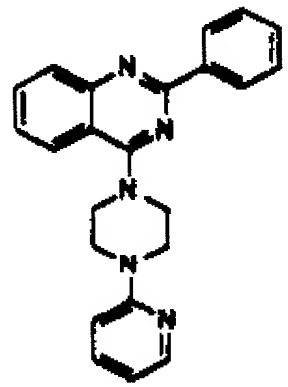

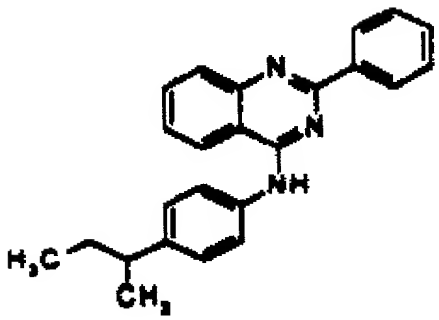

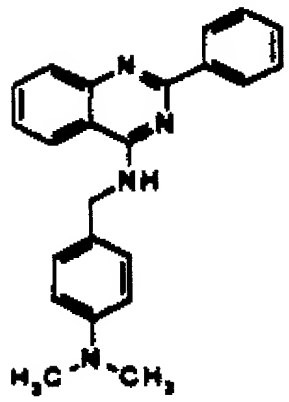

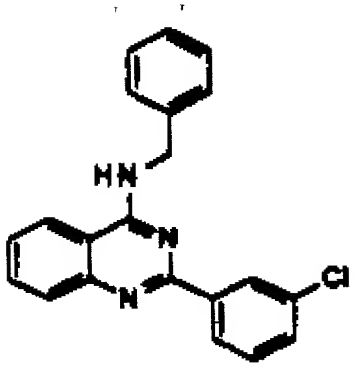

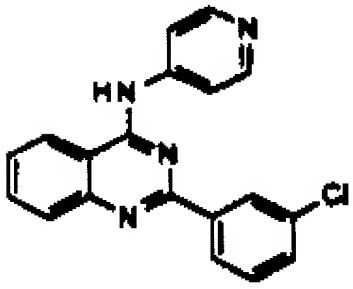

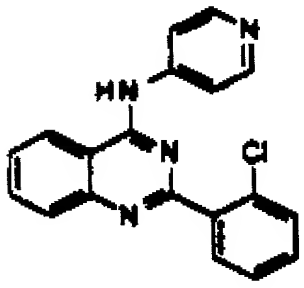

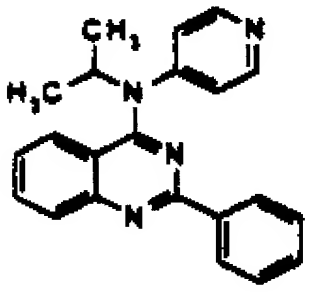

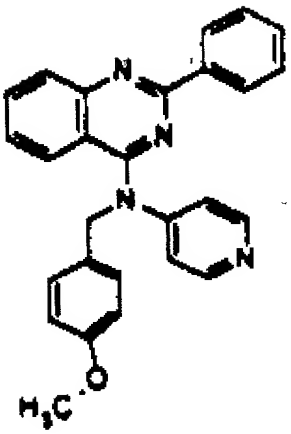

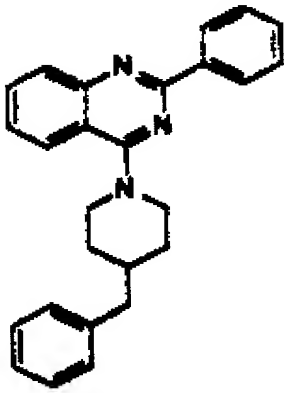

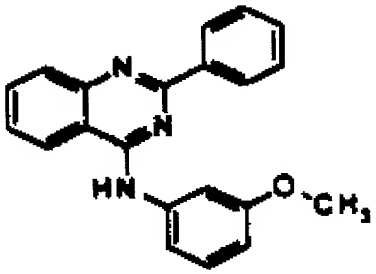

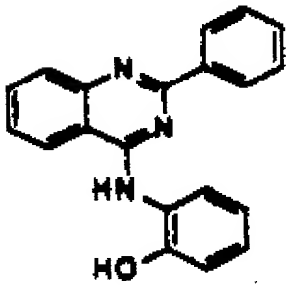

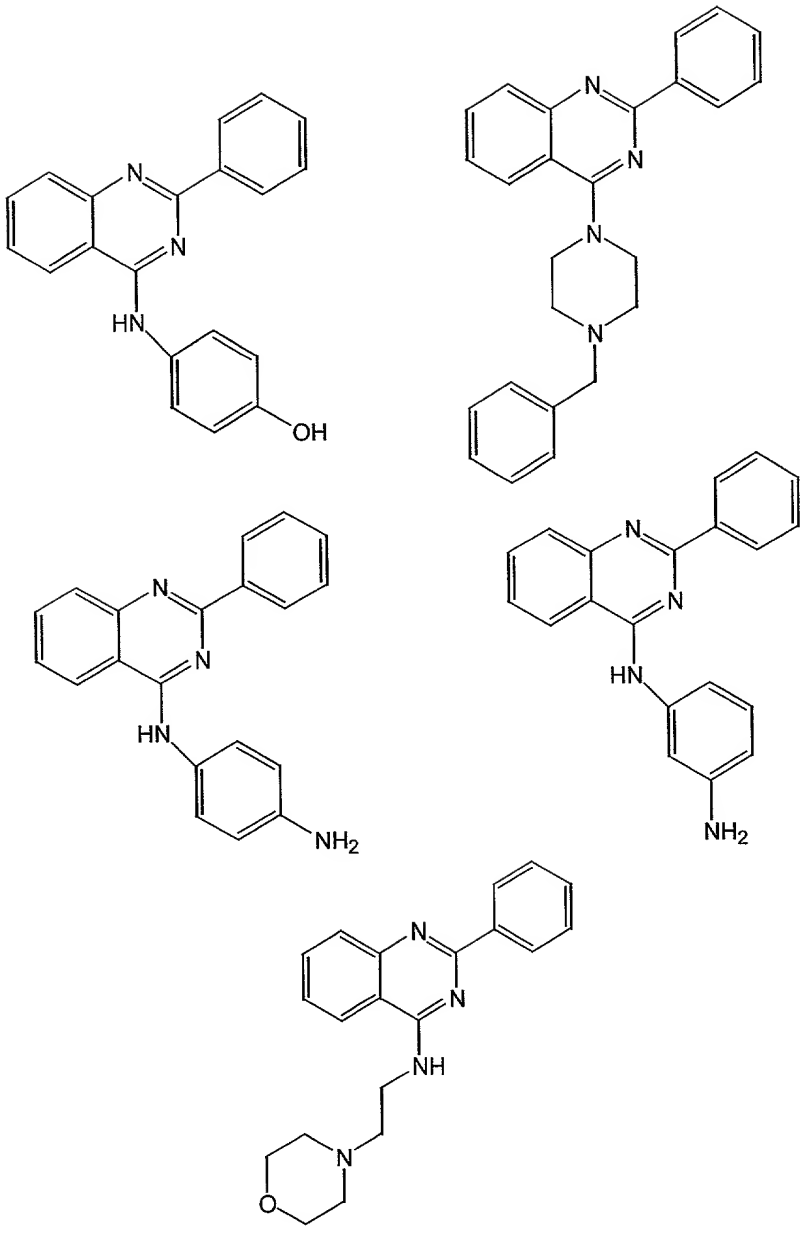

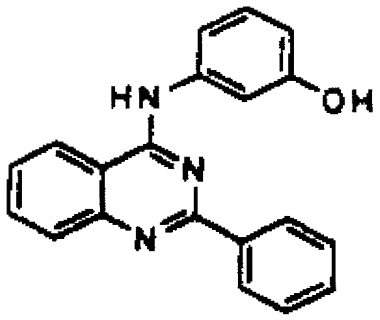
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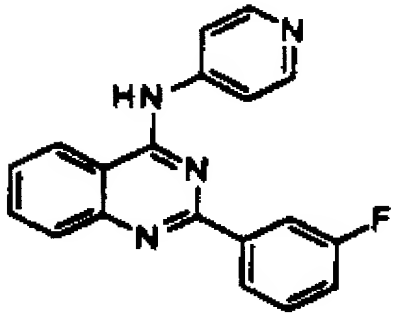
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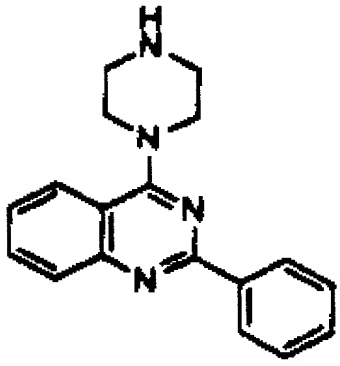
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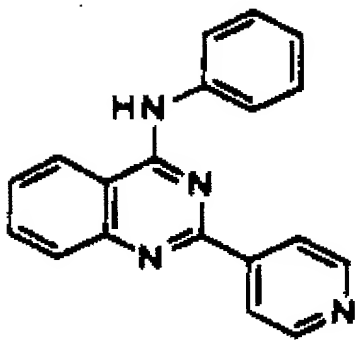
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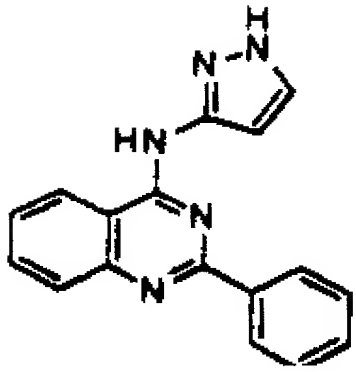
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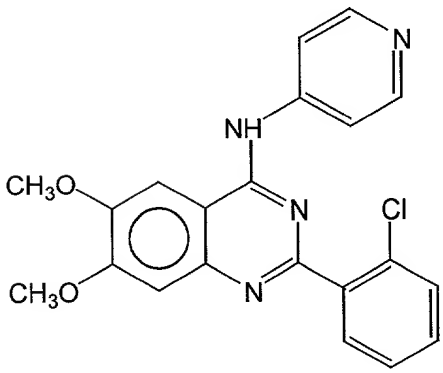
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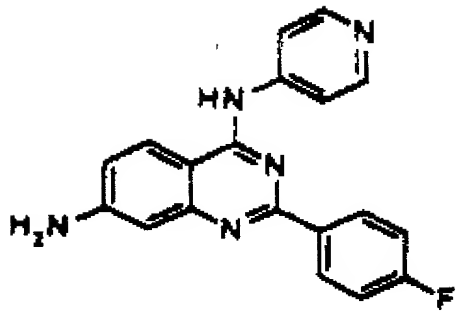
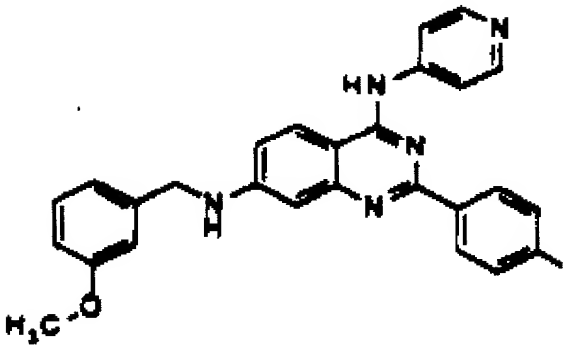
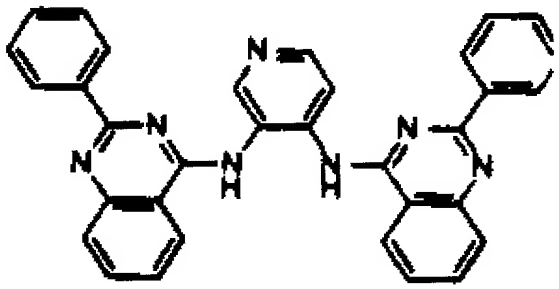
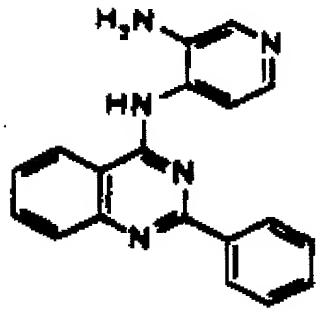
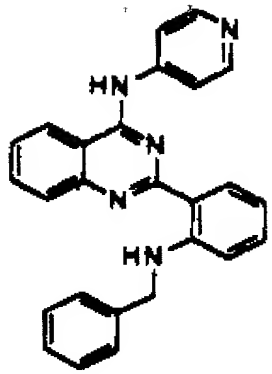
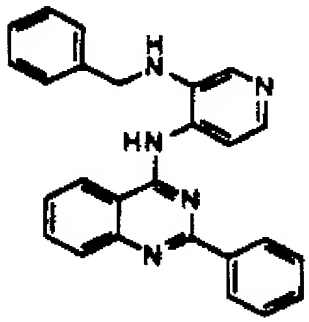


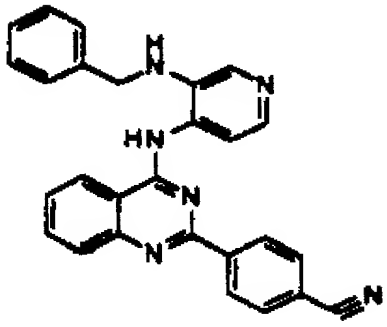


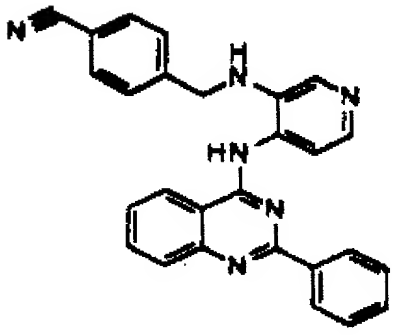


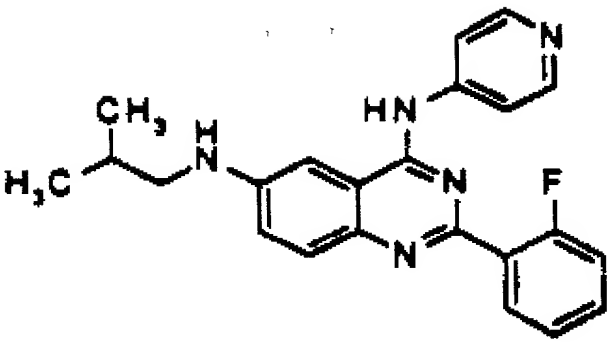


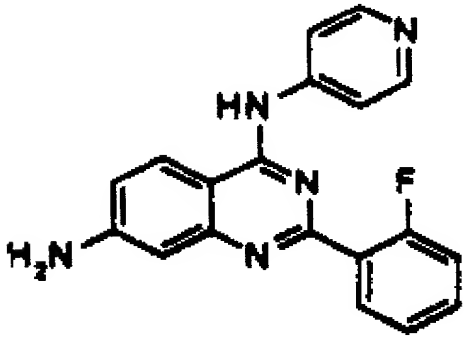


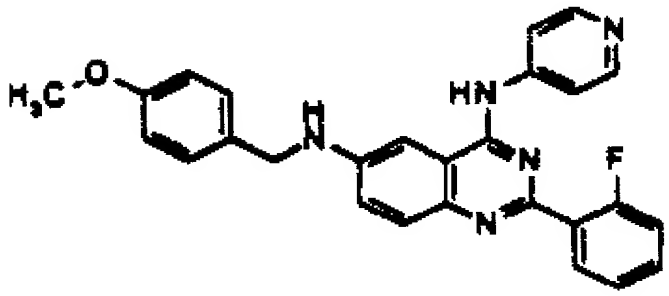


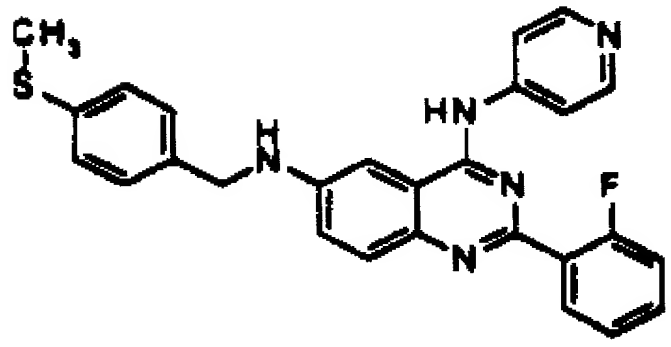


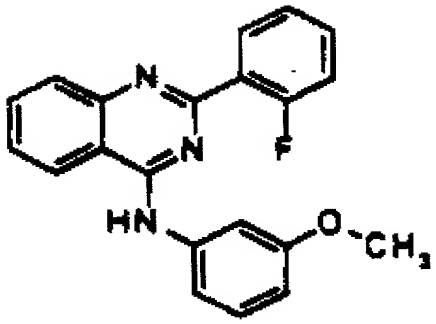


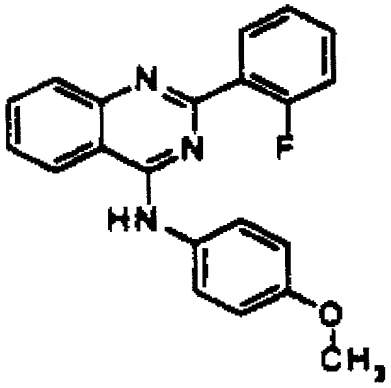


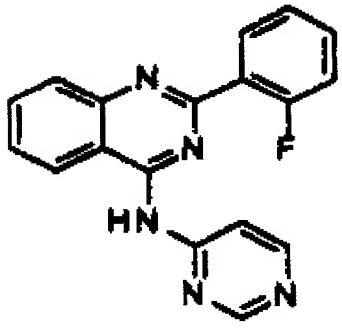


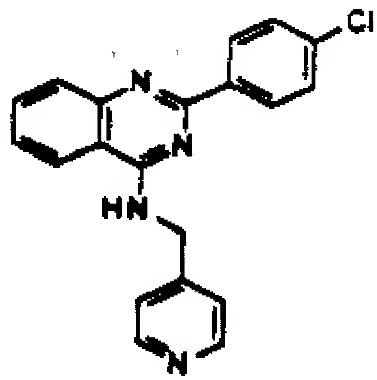


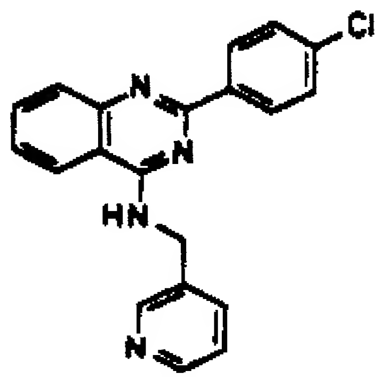


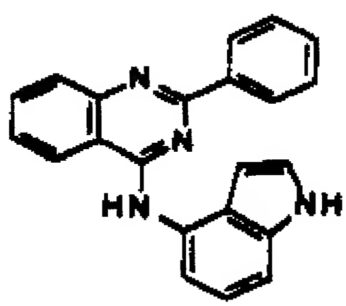


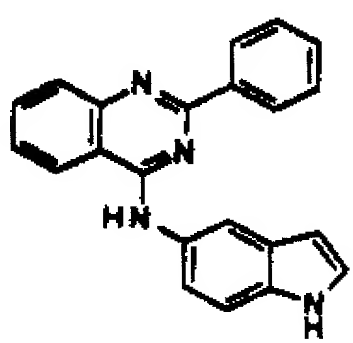


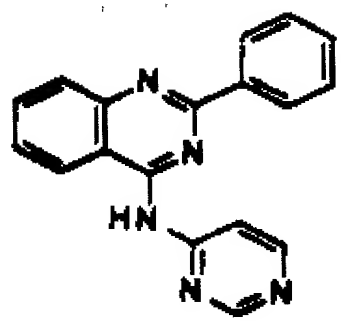


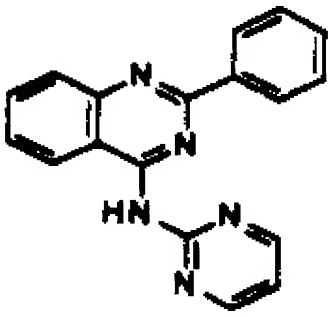


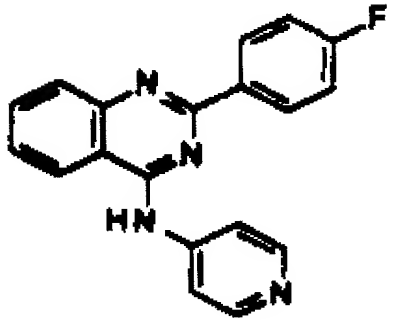


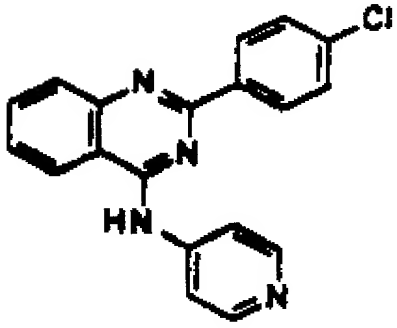












32. (New) The composition of claim 18 wherein

L is $-R^1N(CH_2)_n-$;

L is $-R^1N(CH_2)_n-$ wherein R^1 is H or is alkyl (1-6C) or arylalkyl optionally substituted on the aryl group with 1-3 substituents independently selected from alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, $-SO_2NR_2$, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C) and n is 0, 1 or 2; and

(a) Ar′ is phenyl, substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C), or pyridyl, indolyl, or pyrimidyl, each optionally substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is phenyl optionally substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, $-SO_2NR_2$, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or

(b) Ar′ is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is phenyl substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, $-SO_2NR_2$, CN, and CF_3, wherein each R is independently H or lower alkyl (1-4C); or

(c) Ar′ is phenyl substituted with a group selected from the group consisting of optionally substituted NR_2, SR, -NROCR, RCO, $-CONR_2$, SO_2NR_2, CN, and CF_3, wherein each R is independently H or lower alkyl (1-4C); or pyridyl substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or indolyl or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR,

-NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is phenyl optionally substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, -SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or

(d) Ar' is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is phenyl substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, -SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C).

33. (New) The composition of claim 18 wherein the compound of formula 1 is selected from the group consisting of

2-phenyl-4-(4-pyridylamino)-quinazoline;

2-(2-bromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-chlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-methylphenyl)-4-(4-pyridylamino)-quinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(3-methoxyanilyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-dichlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-dibromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-difluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-nitroquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino -6-aminoquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-7-aminoquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(3-methoxybenzylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methoxybenzylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(2-isobutylamino)-quinazoline; and

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methylmercaptobenzylamino)-quinazoline.

REMARKS

The claims have been amended to place them in a condition for immediate allowance. As amended, the claims are limited to methods and pharmaceutical compositions for inhibiting p38α kinase activity. These claims are clearly supported by the grandparent application Serial No. 09/141,916 filed 28 August 1998. Accordingly, the publications of Alvi, WO 99/18942 and Schindler, WO 99/32460 cited in the parent application are not citable with respect to these claims as their publication dates are subsequent to the priority to which these claims are entitled. Accordingly, it is believed that the proposed claims are allowable.

Claims 1, 8-10, 13, 15-17 and 23-24 are claims to methods to inhibit p38α kinase and are similar to those allowed in the parent application with corresponding numbers except that the parent claims are directed to inhibiting p38α kinase and TGFβ in the alternative. As the present claims are entitled to priority from the grandparent application, certain limitations which were inserted into claim 1 in the parent application to expedite allowance are clearly unnecessary in the present case. Because, however, these claims are simply of different scope, a terminal disclaimer is enclosed.

Also, unlike the parent, composition claims 18-20 have been retained. New claims 25-33 are dependent claims directed to the compositions and are analogous to the claims dependent on the method of claim 1.

Accordingly, no new matter has been added; the general format of the composition and method claims is similar.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to

charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 219002028402. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

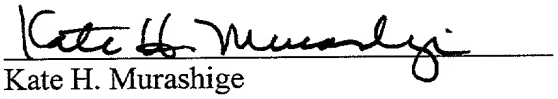
Dated: October 4, 2001 By: 

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

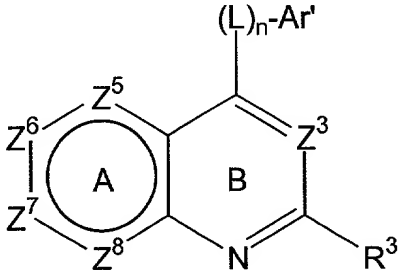
In the Specification:

On page 10, the second paragraph, at lines 5-21:

Each R^2 is also independently a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N. Preferably, R^2 is independently H, alkyl, alkenyl, alkynyl, acyl or hetero-forms thereof or is aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, NRSOR, $NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, NRSOR, $NRSO_2R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C). The aryl or aroyl groups on said substituents may be further substituted by, for example, alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C). More preferably the substituents on R^2 are selected from R^4, halo, OR^4, $NR^4{}_2$, SR^4, $-OOCR^4$, [$-NROCR^4$] $\underline{-NR^4OCR^4}$, $-COOR^4$, R^4CO, $-CONR^4{}_2$, $-SO_2NR^4{}_2$, CN, CF_3, and NO_2, wherein each R^4 is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R^4 or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

In the Claims:

1. (Amended) A method to [treat conditions characterized by enhanced] inhibit p38-α activity[and/or enhanced TGF-β activity], which method comprises [administering to a subject in need of such treatment] contacting said p38-α with a compound of the formula:



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3 [is a noninterfering substituent] comprises a substituted or unsubstituted aromatic moiety, wherein said aromatic moiety is a monocyclic or fused bicyclic moiety containing 5-12 ring member atoms, optionally comprising one or more heteroatoms selected from O, S and N;

each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

each R^2 is [independently a noninterfering substituent;

L is a linker;] either

(i) independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyl, wherein each of alkyl, alkenyl, alkynyl and acyl may optionally contain 1-2 O, S or N, aryl, and arylalkyl, each of said aryl and arylalkyl optionally containing 1 or more O, S or N and wherein in each of the foregoing other than H may be unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C), and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR,

-NRSOR, -$NRSO_2R$, -$OCONR_2$, RCO, -COOR, -SO_3R, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C), or

(ii) independently selected from the group consisting of halo, OR, NR_2, SR, -SOR, -SO_2R, -OCOR, -NRCOR, -$NRCONR_2$, -NRCOOR, NRSOR, $NRSO_2R$, -$OCONR_2$, RCO, -COOR, -SO_3R, NRSOR, $NRSO_2R$, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C);

n is 0 or 1; and

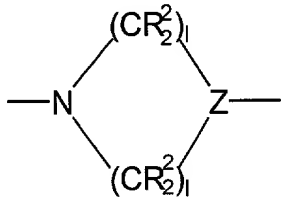
Ar' is [the residue of] a cyclic aliphatic, cyclic heteroaliphatic[,] or a monocyclic or polycyclic aromatic [or heteroaromatic] moiety any of the foregoing optionally substituted with 1-3 [noninterfering] substituents, wherein two of said substituents may form a 5-7 member cyclic optionally heterocyclic aliphatic ring and wherein Ar' and any said substituents thereon forming a cyclic aliphatic ring, may optionally contain one or more ring atoms selected from O, S and N.

8. (Amended) The method of claim [7] 1 wherein [said] any substituents on the aromatic or heteroaromatic moiety of R^3 are independently selected from the group consisting of halo, OR, NR_2, SR, -SOR, -SO_2R, -OCOR, -NRCOR, -$NRCONR_2$, -NRCOOR, -NRSOR, -$NRSO_2R$, -$OCONR_2$, RCO, -COOR, -SO_3R, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C) and [with respect to any aryl or heteroaryl moiety, said group further including] alkyl (1-6C).

10. (Amended) The method of claim 9 wherein Ar' is phenyl, 2-, 3-, or 4-pyridyl, 2- or 4-pyrimidyl, indolyl, isoquinolyl, quinolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzofuranyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, or imidazolyl, [or morpholinyl,] all of which may optionally be substituted.

13. (Amended) The method of claim [11] 1 wherein said optional substituents on R^2 are independently selected from the group consisting of R^4, halo, OR^4, NR^4_2, SR^4, -$OOCR^4$, -$NROCR^4$, -$COOR^4$, R^4CO, -$CONR^4_2$, -$SO_2NR^4_2$, CN, CF_3, and NO_2, wherein each R^4 is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R^4 or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

15. (Amended) The method of claim [14] 1 wherein L is $S(CR^2_2)_m$, $-NR^1SO_2(CR^2_2)_l$, $SO_2(CR^2_2)_m$, $SO_2NR^1(CR^2_2)_l$, [$NR^3(CR^2_2)_m$] $NR^1(CR^2_2)_m$, $NR^1CO(CR^2_2)_l$, $O(CR^2_2)_m$, or $OCO(CR^2_2)_l$, or



wherein Z is N or CH and wherein m is 0-4 and l is 0-3;

R^1 is H, alkyl or arylalkyl where the aryl moiety may be substituted by 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C);

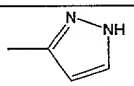
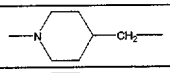
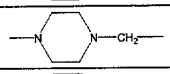
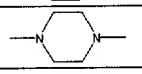
and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C); and

R^2 is as defined in claim [12] 1.

16. (Amended) The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of [compounds 1-87 herein]

(a) the compounds listed in Table 2 below, wherein Z^5-Z^8 are CH; Z^3 is N; R^1 in compound No. 11 is 2-propyl; R^1 in compound No. 12 is 4-methoxyphenyl, and R^1 in compound No. 41 is 4-methoxybenzyl; and wherein L, Ar' and R^3 are as shown in Table 2:

Table 2			
Compound No.	**L**	**Ar'**	**R^3**
1	NH	4-pyridyl	2-chlorophenyl
2	NH	4-pyridyl	2,6-dichlorophenyl
3	NH	4-pyridyl	2-methylphenyl
4	NH	4-pyridyl	2-bromophenyl
5	NH	4-pyridyl	2-fluorophenyl
6	NH	4-pyridyl	2,6-difluorophenyl
7	NH	4-pyridyl	phenyl
8	NH	4-pyridyl	4-fluorophenyl
9	NH	4-pyridyl	4-methoxyphenyl
10	NH	4-pyridyl	3-fluorophenyl
11	NR^1	4-pyridyl	phenyl
12	NR^1	4-pyridyl	phenyl
13	$NHCH_2$	4-pyridyl	phenyl
14	$NHCH_2$	4-pyridyl	4-chlorophenyl
15	NH	3-pyridyl	phenyl
16	$NHCH_2$	2-pyridyl	phenyl
17	$NHCH_2$	3-pyridyl	phenyl
18	$NHCH_2$	2-pyridyl	phenyl
19	$NHCH_2CH_2$	2-pyridyl	phenyl
20	NH	6-pyrimidinyl	phenyl
21	NH	2-pyrimidinyl	phenyl
22	NH	Phenyl	phenyl
23	$NHCH_2$	Phenyl	3-chlorophenyl
24	NH	3-hydroxyphenyl	phenyl
25	NH	2-hydroxyphenyl	phenyl
26	NH	4-hydroxyphenyl	phenyl
27	NH	4-indolyl	phenyl
28	NH	5-indolyl	phenyl
29	NH	4-methoxyphenyl	phenyl
30	NH	3-methoxyphenyl	phenyl
31	NH	2-methoxyphenyl	phenyl
32	NH	4-(2-hydroxyethyl)phenyl	phenyl
33	NH	3-cyanophenyl	phenyl
34	$NHCH_2$	2,5-difluorophenyl	phenyl
35	NH	4-(2-butyl)phenyl	phenyl
36	$NHCH_2$	4-dimethylaminophenyl	phenyl

Table 2			
Compound No.	**L**	**Ar'**	**R^3**
38	NH	2-pyridyl	phenyl
39	$NHCH_2$	3-pyridyl	phenyl
40	NH	4-pyrimidyl	phenyl
41	NR^1	4-pyridyl	phenyl
42	NH	p-aminomethylphenyl	phenyl
43	$NHCH_2$	4-aminophenyl	phenyl
44	NH	4-pyridyl	3-chlorophenyl
45	NH	Phenyl	4-pyridyl
46	NH		phenyl
48	NH	2-benzylamino-3-pyridyl	phenyl
49	NH	2-benzylamino-4-pyridyl	phenyl
50	NH	3-benzyloxyphenyl	phenyl
51	NH	4-pyridyl	3-aminophenyl
52	NH	4-pyridyl	4-pyridyl
53	NH	4-pyridyl	2-naphthyl
54		4-pyridyl	phenyl
55		Phenyl	phenyl
56		2-pyridyl	phenyl
61	NH	4-pyridyl	2-trifluoromethyl phenyl
62	NH	4-aminophenyl	phenyl
64	NH	3-methoxyphenyl	2-fluorophenyl
65	NH	4-methoxyphenyl	2-fluorophenyl
66	NH	4-pyrimidinyl	2-fluorophenyl
67	NH	3-amino-4-pyridyl	phenyl
68	NH	4-pyridyl	2-benzylaminophenyl
69	NH	2-benzylaminophenyl	phenyl
70	NH	2-benzylaminophenyl	4-cyanophenyl
71	NH	3'-cyano-2-benzylaminophenyl	phenyl

(b) the compounds listed in Table 3, below, wherein L is NH; Z^3 is N; Z^6 and Z^7 are CH and Z^5, Z^8, Ar' and R^3 are as shown in Table 3:

Table 3

Compound No.	Z^5	Z^8	Ar'	R^3
72	CH	N	4-pyridyl	2-fluorophenyl
73	CH	N	4-pyridyl	2-chlorophenyl
74	CH	N	4-pyridyl	phenyl
75	N	N	4-pyridyl	phenyl
76	N	CH	4-pyridyl	phenyl

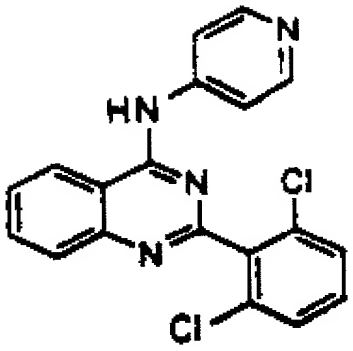
and

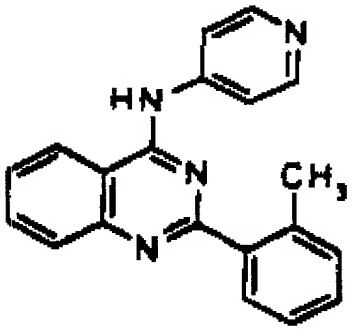
(c) the quinazoline derivatives listed in Table 4 below, wherein L is NH; Ar' is 4-pyridyl; Z^3, Z^5, and Z^8 are N; Z^6 or Z^7 are CR^2 as shown and each is otherwise N and wherein R^3 and R^2 are as shown in Table 4:

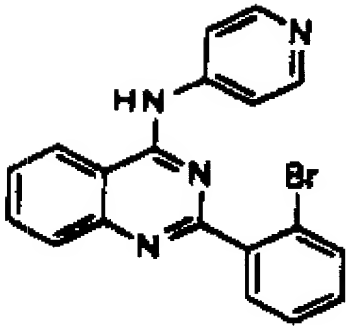
Table 4

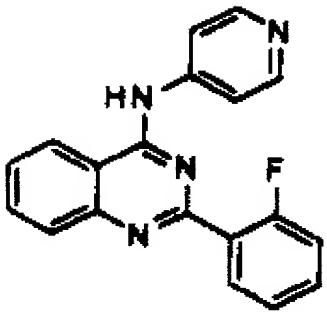
Compound No.	R^3	R^2
77	2-chlorophenyl	6,7-dimethoxy
78	2-fluorophenyl	6-nitro
79	2-fluorophenyl	6-amino
80	2-fluorophenyl	7-amino
81	2-fluorophenyl	6-(3-methoxybenzylamino)
82	2-fluorophenyl	6-(4-methoxybenzylamino)
83	2-fluorophenyl	6-(2-isobutylamino)
84	2-fluorophenyl	6-(4-methylmercaptobenzylamino)
85	2-fluorophenyl	6-(4-methoxybenzoyl amino)
86	4-fluorophenyl	7-amino
87	4-fluorophenyl	7-(3-methoxybenzylamino)

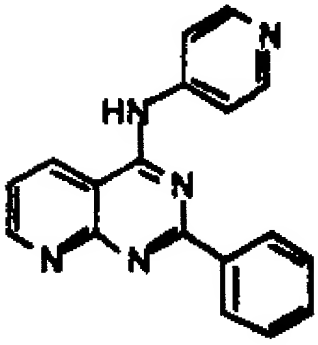
17. (Amended) The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of the following compounds: [shown in Figures 1A-1C herein.]

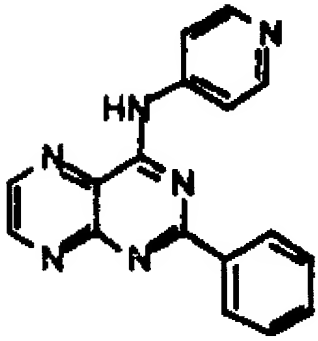


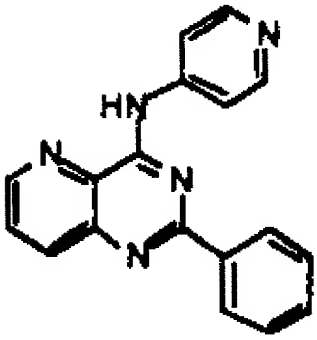


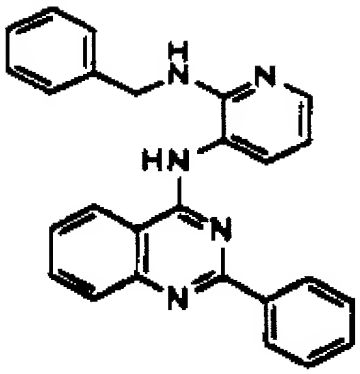


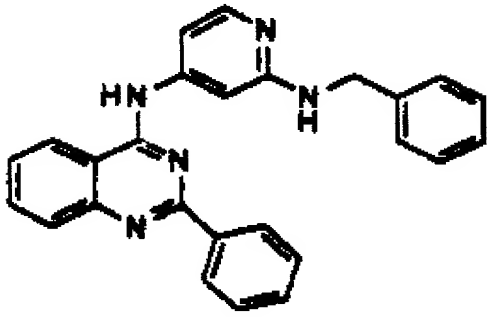


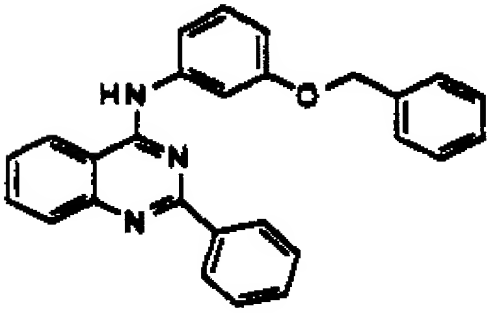


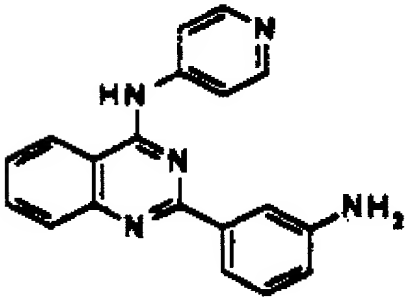


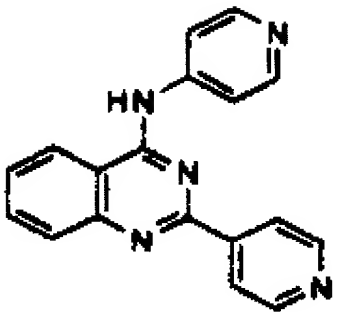


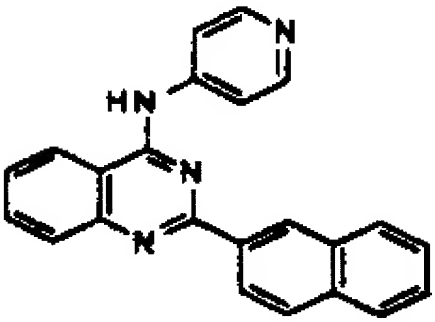


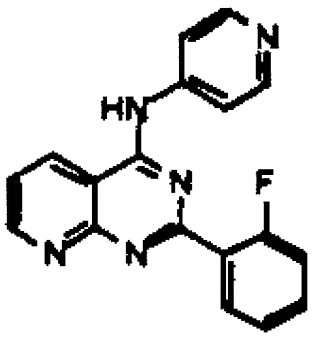


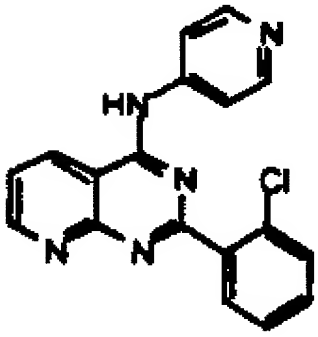


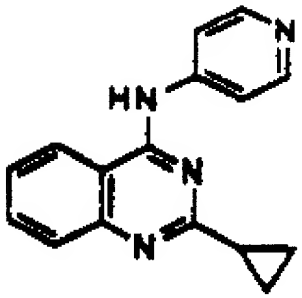


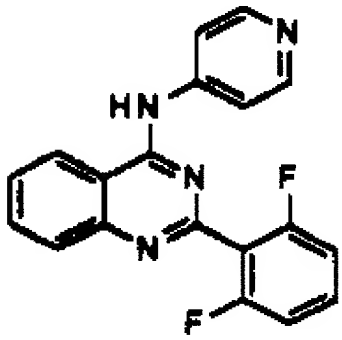


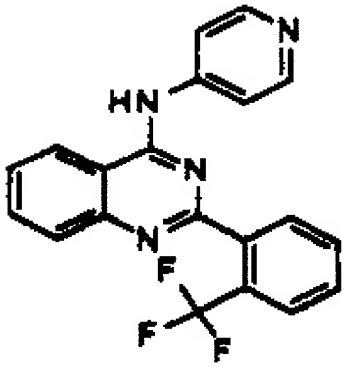


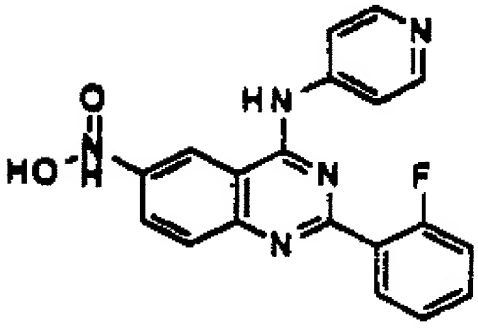


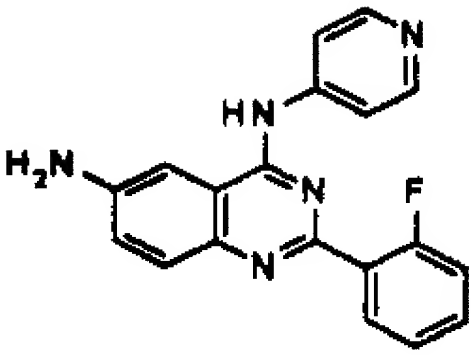


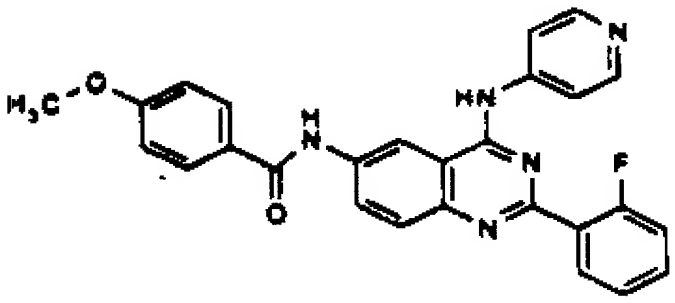


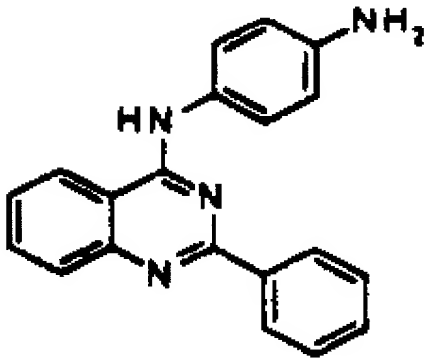


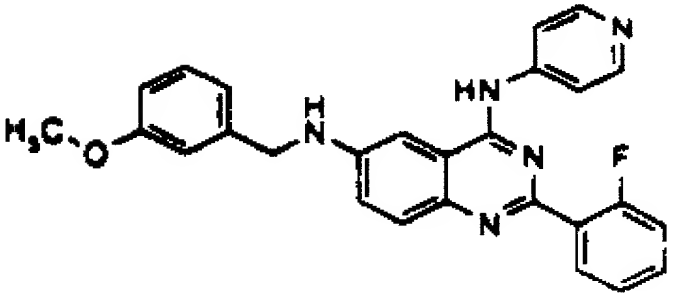


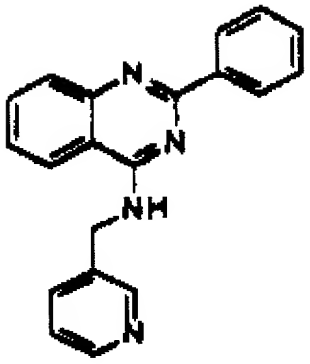


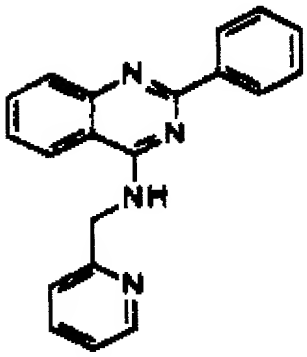


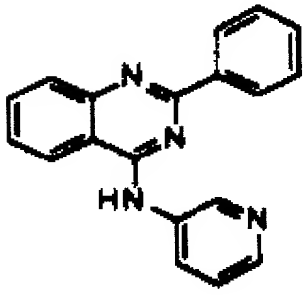


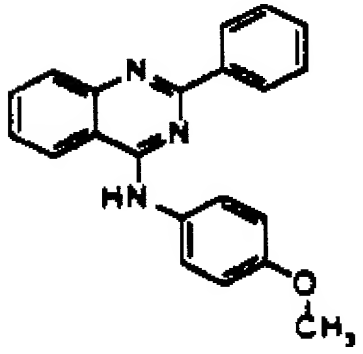


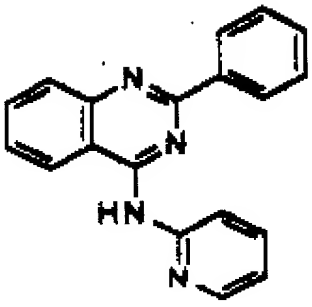


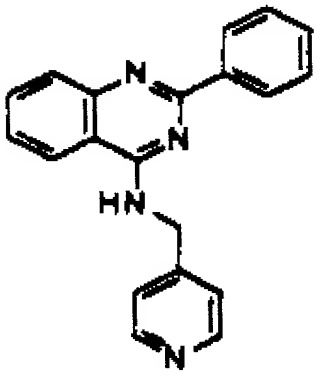


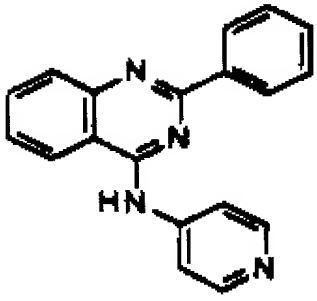


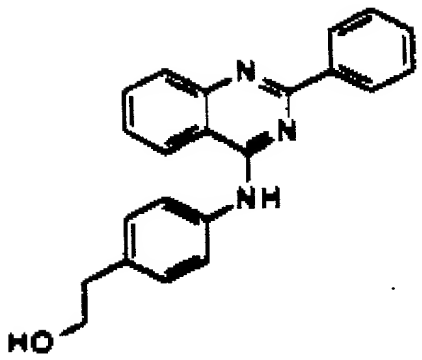


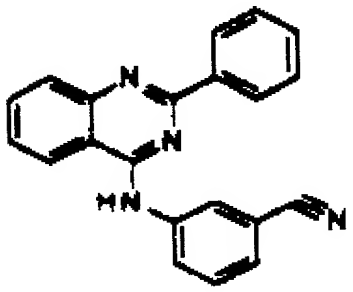


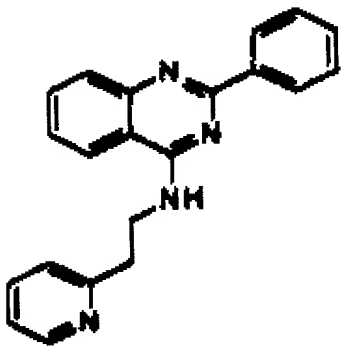


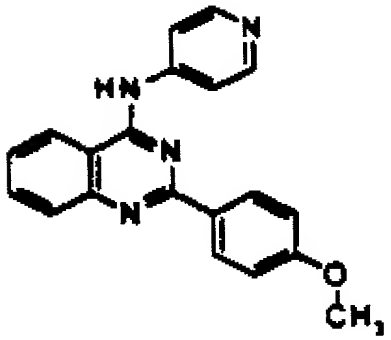


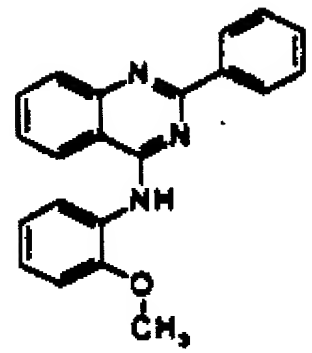


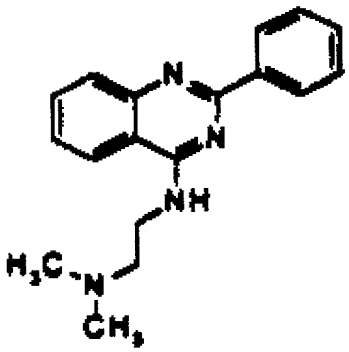


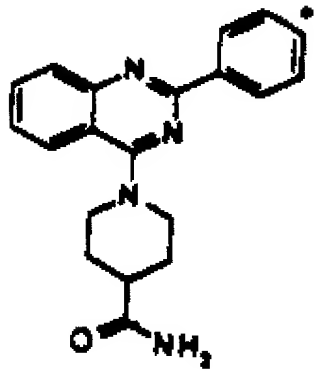


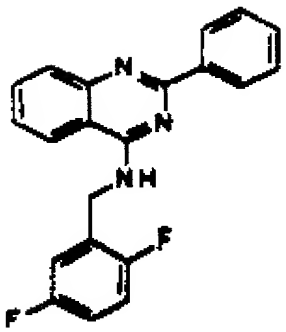


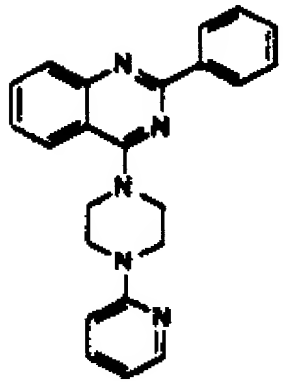


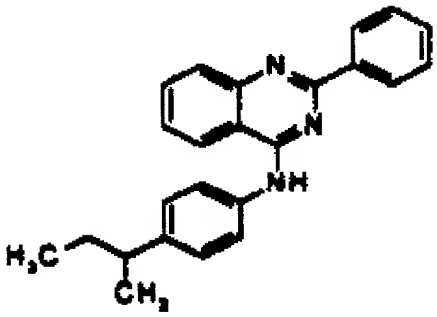


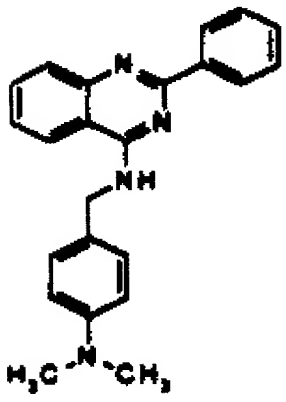


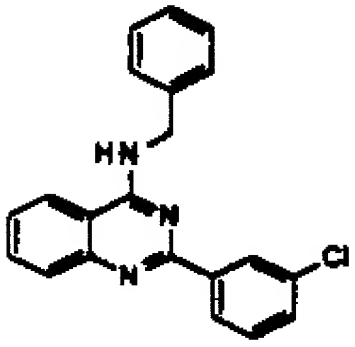


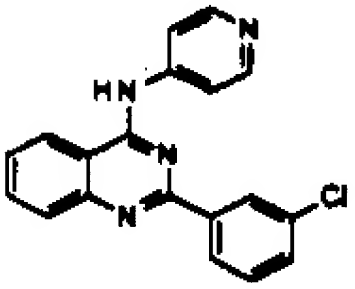


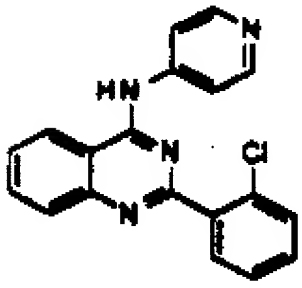


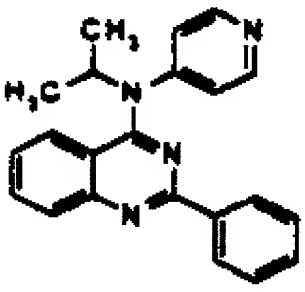


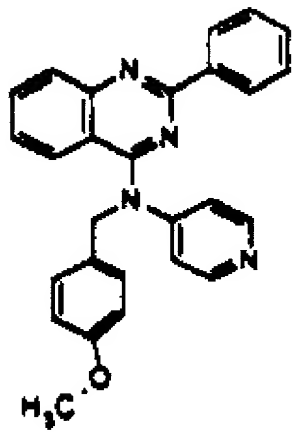












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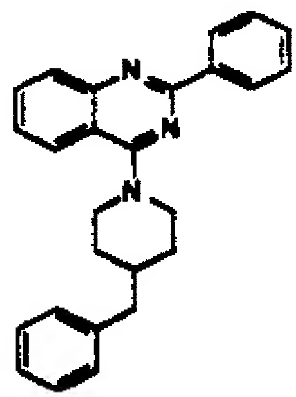

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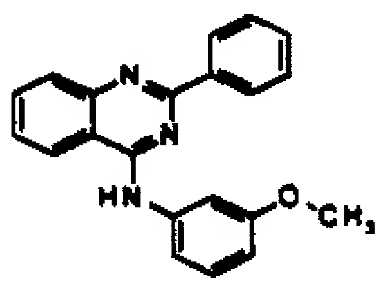

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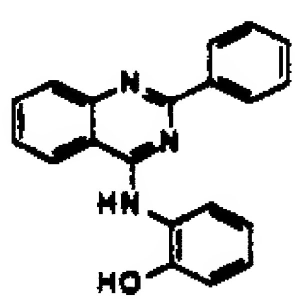

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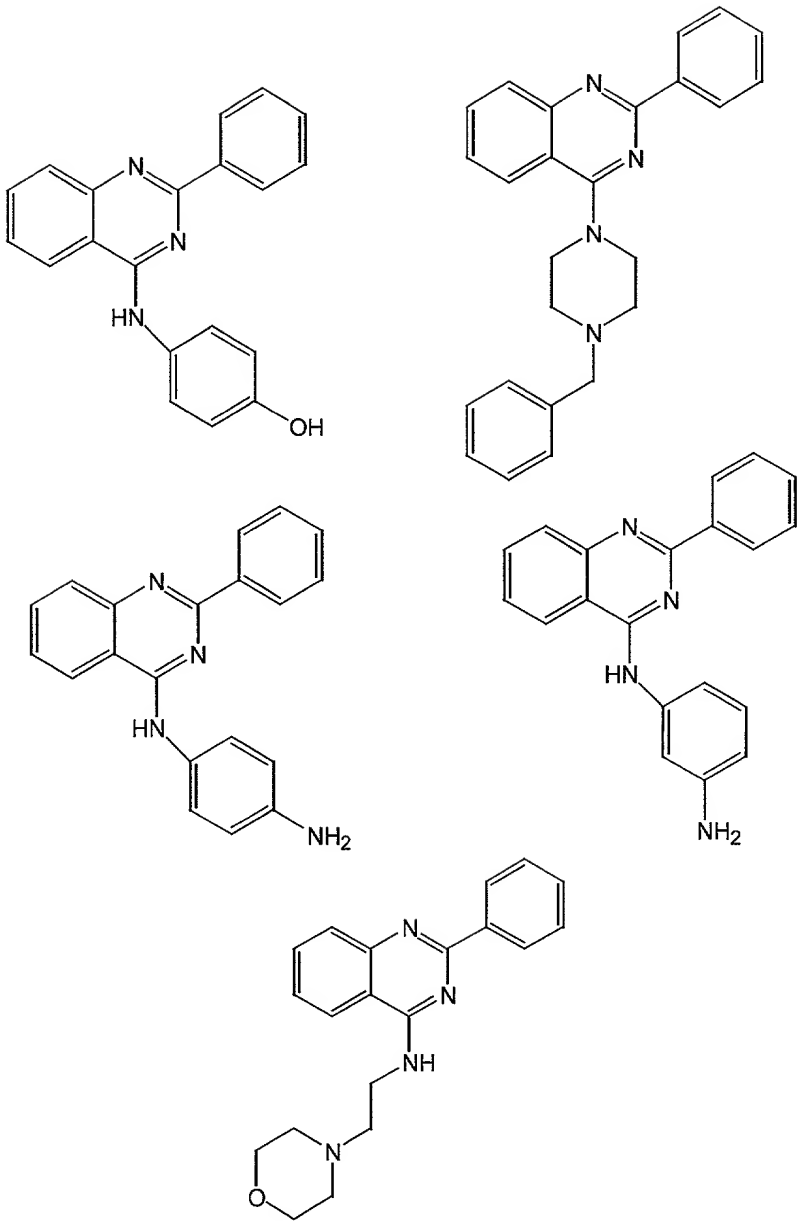

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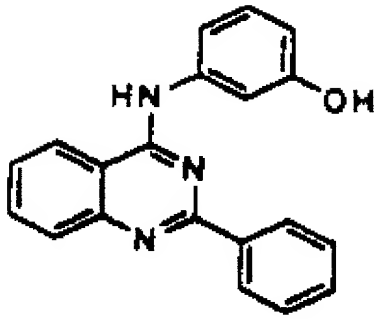
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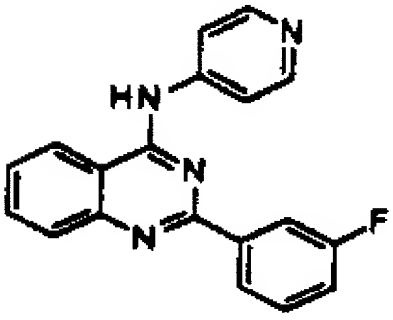
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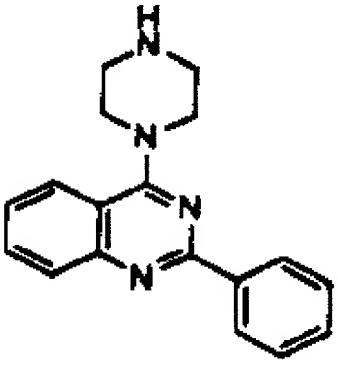
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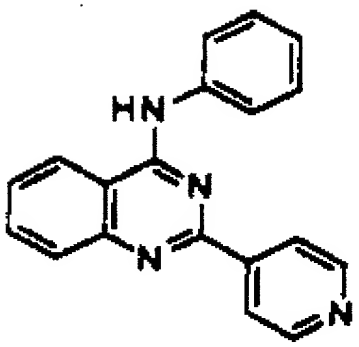

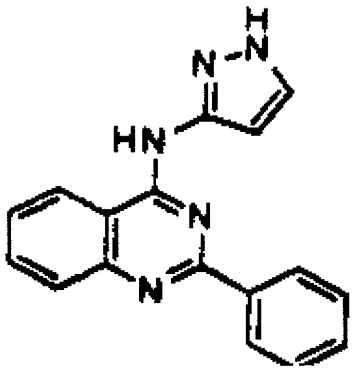

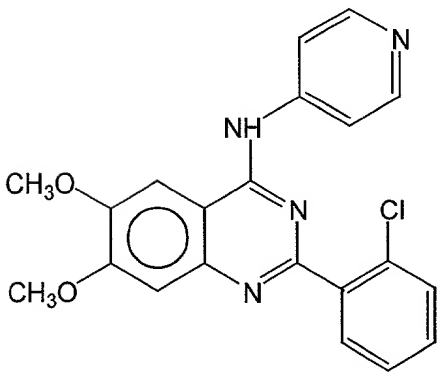

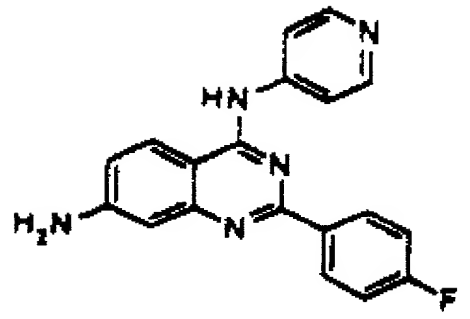

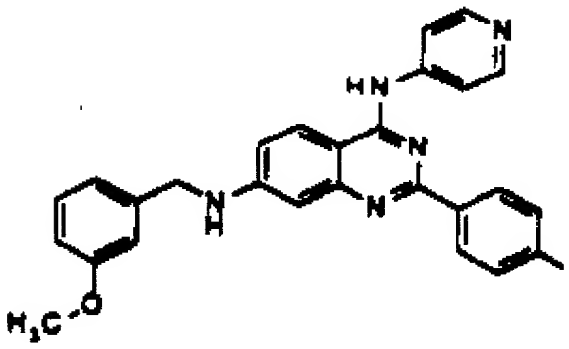

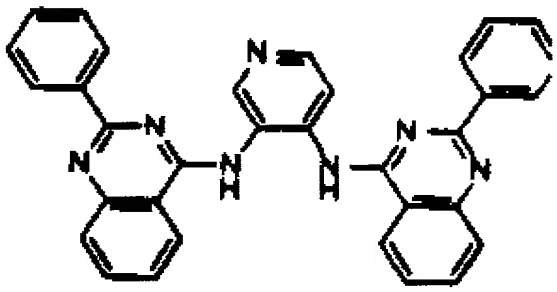

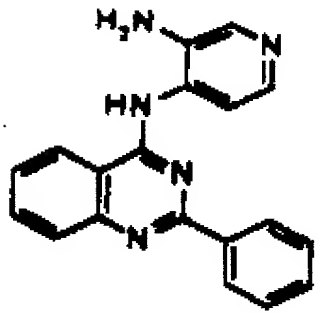

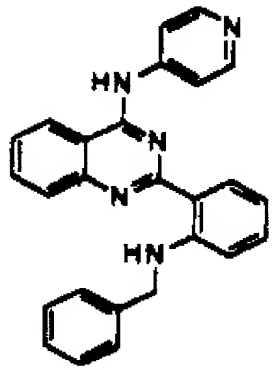

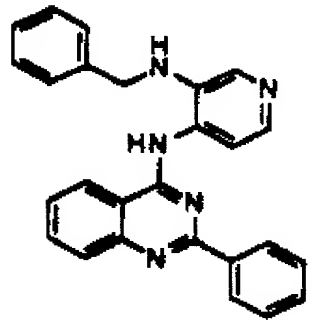

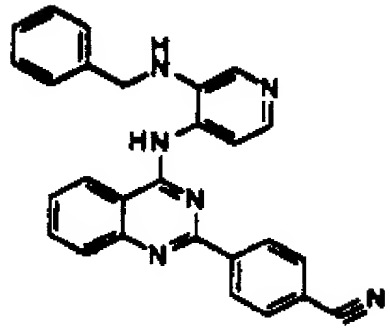

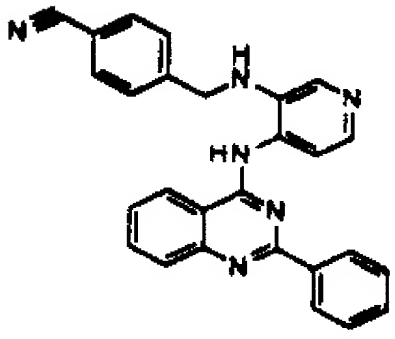

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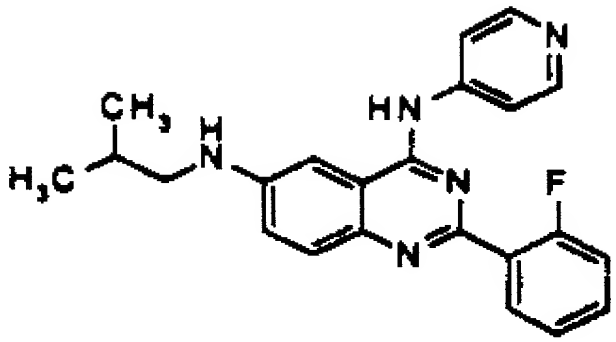

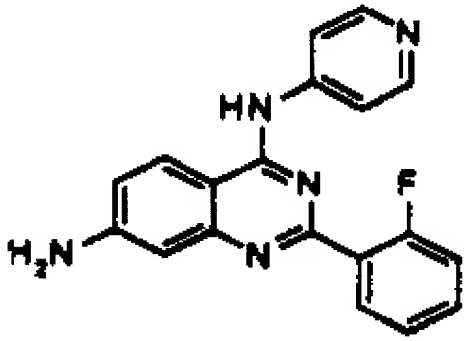

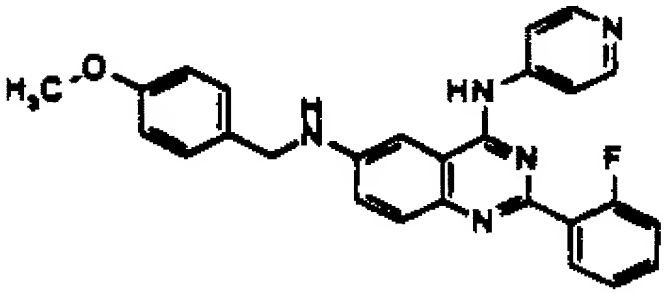

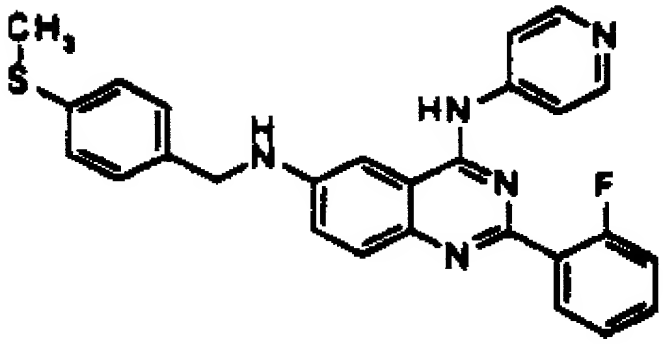

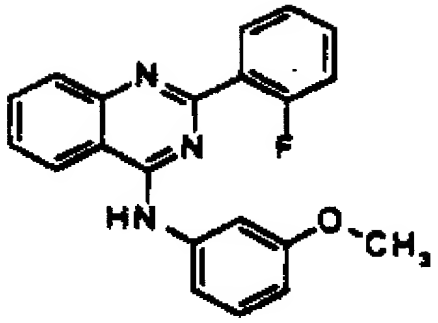

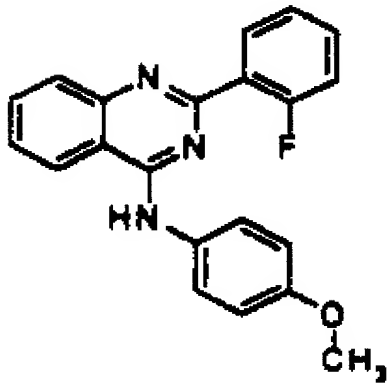

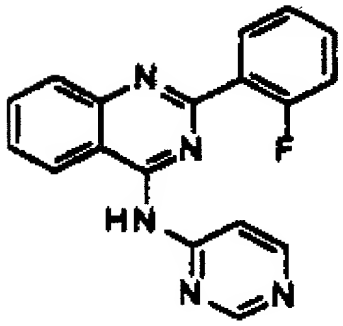

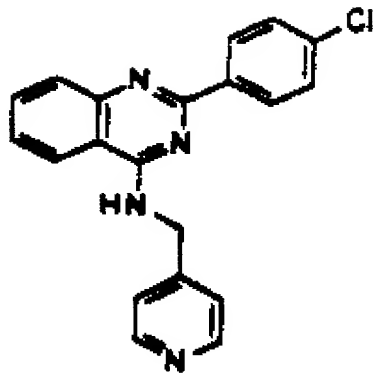

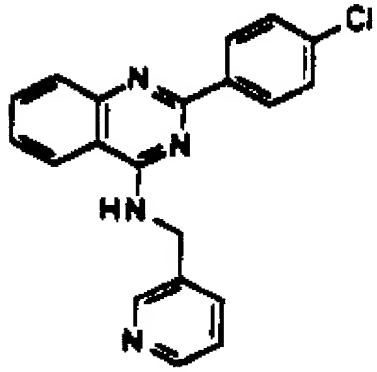

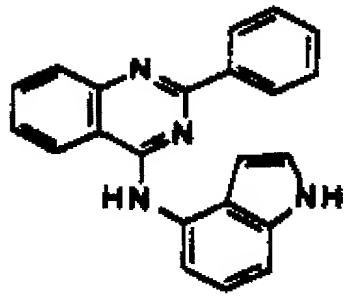

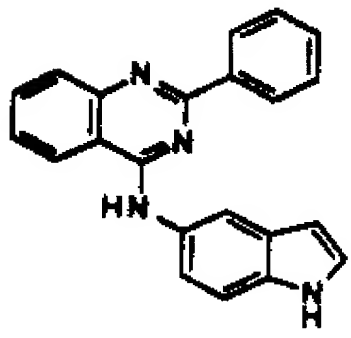

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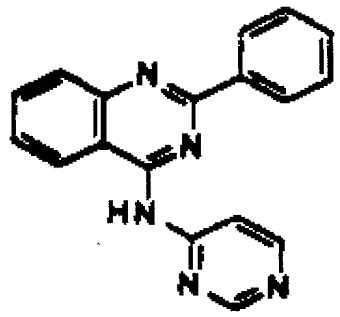
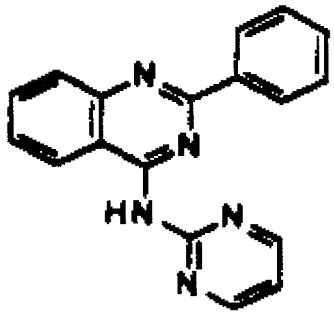
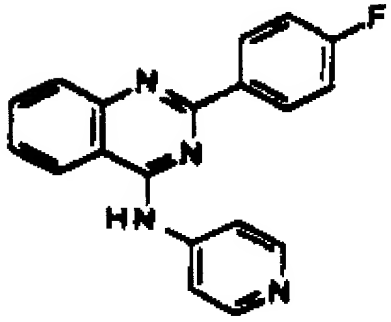
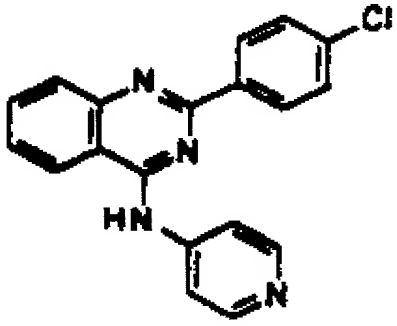


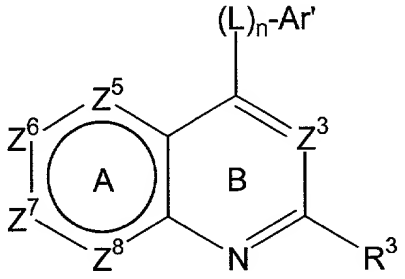






18. (Amended) A pharmaceutical composition for treating conditions characterized by enhanced [p38-α activity and/or enhanced TGF-β] p38α kinase activity which composition comprises

[a therapeutically effective] an amount of a compound of the formula



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3 [is a noninterfering substituent];

each Z [is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N];

each R^2 [is independently a noninterfering substituent];

L [is a linker];

n [is 0 or 1]; and

Ar' [is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents] are as defined in claim 1 which is effective to inhibit p38α kinase activity in admixture with at least one pharmaceutically acceptable excipient appropriate for administering to a subject exhibiting enhanced p38α kinase activity.